ANNUAL REPORT
OF
PROGRAM ACTIVITIES

NATIONAL INSTITUTES OF HEALTH
1968-1969

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND STROKE
VOL. II

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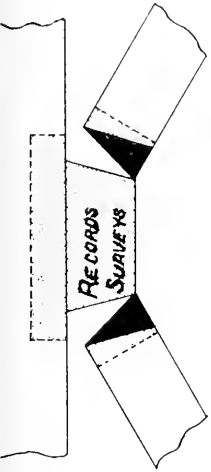

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ANNUAL REPORT
For Period July 1, 1968 through June 30, 1969
Acting Associate Director for Collaborative and Field Research
National Institute of Neurological Diseases and Stroke
National Institutes of Health

INTRODUCTION

I assumed the position of Acting Associate Director for the Collaborative and Field Research Program in September 1968. Since that time we have operated this program as a unit which for the first time includes the Perinatal Research Branch. In addition to our attempts to give this program a sense of unity, we have tried to correlate its individual projects with each other, and where appropriate, with both Intramural and Extramural Program efforts. In order to do this, we reviewed the present programs of the branches and sections and re-evaluated many of them in relationship to the Institute's mission. In view of reduced budgets and personnel ceilings, we established priorities among the different projects. Through all of this effort, we attempted to find out how to better administer the program and strengthen this important part of the Institute's program of direct research. The principal problem in this respect with which we have had to deal is charting the future course of the Institute's Collaborative Perinatal Research Project.

The completion of Building 36 and the move of several of the programs to this facility has been a noteworthy event. Certain of the laboratories, however, need more extensive reconstruction and will probably not be ready for full occupancy until early in 1970. The moves which have taken place have cut down serious overcrowding and enabled these programs to now operate much more efficiently.

A most important event has occurred relating to the future development of field research within the Institutes by the appointment of Dr. Leon Jacobs as Assistant Director for Collaborative Programs in the Office of the Associate Director for Direct Research in the Office of the Director, NIH. We welcome the assistance which the establishment of this office will provide.

In the paragraphs which follow, certain events of significance within the various bronches and programs will be highlighted. No attempt will be made to duplicate information which is given in detail in the individual reports which follow. One thing stands out clearly in all of the individual reports, namely, the increasing effectiveness of the assistance rendered these programs by the Office of Biometry which was recently created in the Office of the Director. This administrative move has clearly demonstrated its worth.

The Perinatal Research Project

This program has been under almost constant review for the last several years. First, by the committee appointed by Dr. James A. Shannon and chaired by Dr. Harry Gordon. Following the report of Dr. Gordon's committee, Dr. Richard Masland, then Director of NINDB, organized a working committee under Dr. Abraham Lilienfeld which completed its report in December 1968. This second report resulted in a series of recommendations which have all been implemented except two which are still under study by the staff and the Perinatal Research Committee. In brief, Dr. Lilienfeld's committee reported the numerous strengths of the information which has been collected in the project. Although some inadequacies were also described, the overwhelming evidence is that the project has resulted in the establishment of a tremendously valuable instrument to study neuropsychiatric development in children as the result of prenatal and perinatal events. During the year, a comprehensive review of data on the study population has been planned and is now being processed. This resultant document will be the first of several designed to describe what the study data contain. In addition, plans for an orderly and systematic detailed analysis of the study data are under development. Through all of these efforts, the Office of Biometry has played a major role. In addition, considerable help has been received from consultant groups outside the project and from the project directors in the various collaborating institutions.

We feel that we have been fortunate in being able to appoint additional members to strengthen the Perinatal Research Committee. We have clarified the Committee's role as an advisory group to the Chief of the Perinatal Research Branch, the Associate Director and the Institute Director; in the provision of systematic and objective merit review of study proposals including those from each of the collaborating institutions; and its role in the surveillance of the performance of the individual contracts.

The change of the Perinatal Project from a research grants operation with the collaborating institutions to one funded by contracts with more direct supervision by the Perinatal Research Branch resulted in many problems, not the least of which is the relationship of Project Directors with the Perinatal Research Branch Staff. Strong efforts are being made to solve the difficulties.

There are a number of exciting results of the project's studies which will be described in the reports which follow, however, at this point, it is pertinent to point out several of them. The first is the identification of a form of measles virus as a cause of subacute sclerosing panencephalitis. The demonstration of this relationship opens an avenue of research in respect to the etiology of other diseases of the nervous system such as multiple sclerosis. The second is the demonstration that Rubella causes certain serious damage in the infants not only in the first trimester of pregnancy, but also in the second trimester. Still another worthy of mention is the relationship demonstrated between pre-pregnancy weight, weight gain during pregnancy, and the birthweight of the baby. The latter study has important implications for the various obstetric practices of control of weight during pregnancy.

The future of the Perinatal Project is one of promise. In order to take full advantage of the opportunities, the Branch is being reorganized administratively to more clearly fulfill its present role of quality control of data, data analysis, and contracts management. Full use will be made of project directors and others in the collaborating institutions, and of outside consultants in addition to staff of the Branch in the conduct of data analysis and special studies.

Special Chronic Disease Studies

The studies of neurologic development and its disorders in primitive cultures continues to provide an unusual opportunity for the study of disease patterns in isolated groups of individuals. In the studies of Kuru, the search for additional animals to the chimpanzee in whom the disease is transmissible, resulted this year in success when Kuru was successfully transmitted to several spider monkeys. Kuru was the first subacute and chronic degenerative disease of the central nervous system in man in which there was developed a transmission model in the chimpanzee. During the year our staff successfully transmitted Creutzfeldt-Jakob disease, a type of spongioform encephalopathy to chimpanzees. These successes continue as a most exciting breakthrough opening the way to the study of other transmissible agents as the cause of degenerative diseases of the nervous system.

As a by-product of the study of neurologic disease in primitive cultures the staff was able to demonstrate a new response to influenza vaccine in populations which have no previous experience with this disease.

These are a few of the highlights of one of the Institute's most productive programs which it is proposed to raise to Branch status during the coming year.

Special Projects Branch

This Branch has two sections--one on Epilepsy and the other on Head Injury. During the year, the Chief of the Section on Epilepsy also assumed directorship of the Institute's Head Injury Program. In the epilepsy program the collaborative study of petit mal has been completed and the writing of reports are well advanced. Other drug studies have been developed at New Castle State Hospital, the University of Virginia Hospital, and the Marquette University School of Medicine. A great deal of meticulous design has gone into the development of the protocols for these studies.

The Chief of the Section on Epilepsy has also assumed the position of Executive Secretary of the Public Health Service Advisory Committee on the Epilepsies. This Committee has had additional members appointed and its role more clearly defined. Very active subcommittees within the Committee have continued productive activities. The holding of the Symposium on the Basic Mechanisms in Epilepsy and the development of this report are worthy of special mention. It is felt that this activity particularly had outstanding success.

Another advisory committee has been appointed during the year, namely, an ad hoc Committee on Anticonvulsant Drugs. This Committee has had a most successful meeting and given clear direction to the Institute for its future studies of anticonvulsant drugs.

In the Head Injury Program the questionnaire survey of Korean War Veterans by the Red Cross has been completed. The data are now being analyzed and the final report is expected during the fall of 1969. This should provide information on the work status and the prevalence of post-traumatic syndrome and epilepsy in these veterans who suffered head injury.

The Head Model Construction Project has progressed satisfactorily with the highly competent and interested assistance of the Head Model Construction Committee. Recently, the early results of the studies have enabled the Institute to now provide more precise direction and supervision to the institutions with whom we have contracts to construct the model. Fortunately, we have been able to obtain the services of Dr. Ayub Ommaya as technical advisor to the project.

An indepth analysis of the state of the art in respect to head injury research is now underway. With the results of this study and with the help of professional help it is our intention to develop a research plan for the Institute.

Epidemiology

Studies of Amyotrophic Lateral Sclerosis and Parkinson-Dementia continue to be a major concern of this Branch, particularly, attempts to clarify the reasons for the unusually high incidence of these diseases on the Island of Guam. There is no evidence of any decline in this incidence. A high prevalence rate of epilepsy has also been noted. A chronic problem in the Guam studies has been our inability to get the necessary neuropathological examination of brain specimens conducted. It now appears that this problem has been solved.

The Branch has also been concerned with the development of long-term studies of the chronic effects of the administration of L-DOPA in Parkinson's disease. These studies are being developed with the cooperation of the Office of Biometry. Another major concern of our epidemiology studies is in the field of stroke in which additional studies are in the planning stage. Two major efforts of the Genetics Section are the clinical and biochemical studies of movement disorders; and the genetic and clinical evaluations of acoustic neuroma.

The Ophthalmology Section continues to carry out with success its studies in twins of the heritability of the effect of cortical steroids on intra-ocular pressure. This program will be one that is transferred to the National Eye Institute at the appropriate time.

CONCLUSIONS

It is clear that this Institute has a collaborative and field research program which has elements of excellence. On the other hand, there is evidence that some portions need revised objectives and closer correlation with what the Institute is doing or supporting in its Intramural and Extramural Programs to solve particular problems of neurologic and sensory diseases and disorders. Its projects must also be related to those of other Institutes and Divisions within the National Institutes of Health, and with other Federal Agencies, for example, the perinatal project, slow virus studies, anticonvulsant studies and the head injury program. In this latter respect, it has liaison problems of greater magnitude than either the Intramural or Extramural Programs and, as a result, demands a different type of direction. The Collaborative and Field Research staff and program should be chosen and designed to provide the Institute Director with flexibility and ability to meet research emergencies and take advantage of research opportunities when it appears that the Institute has a unique role to play.

The Institute's two principal means to conduct direct research are its Intramural and its Collaborative and Field Research Programs. Increased participation of Intramural scientists in the planning and conduct of field research programs would lend considerable strength. This participation, however, is not intended to be of sufficient magnitude to interfere with an Intramural scientist's research efforts but rather to obtain his advice and, one would hope, increase his interest in helping solve the Institute's problems.

ANNUAL REPORT
July 1, 1968 through June 30, 1969
Special Chronic Disease Studies for Collaborative and Field Research
National Institute of Neurological Diseases and Stroke
National Institutes of Health

Study of Child Growth and Development and Disease Patterns in Primitive Cultures; and, Slow, Latent and Temperate Virus Infections

Under this heading the long-term human biology study of many vanishing primitive societies has been under way for 12 years or more. All our laboratory research projects and the numerous collaborating investigators are working on problems which have been phrased under this theme. The neurological development and learning patterns in children in diverse cultural experiments in the human condition has been the major focus of attention. The laboratory studies on human biology, genetics and associated molecular biology, immunology, virology and biochemistry have all been directed at solving problems which have been carefully chosen from small isolated bands still living in the primitive situation in which these problems may be more appropriately studied than in larger, civilized societies.

Our efforts to document the development and neurological patterning in disappearing primitive cultures has resulted in the largest archive of such documentation in the world. The collection and preservation of the existing cinema data from Australian aborigines, New Guinean and African aborigine groups, and American Indians as they live as hunter-gatherers or primitive hoe-and-digging stick agriculturists, provides the only such documentation of the life and behavior of man as he most probably lived and evolved better than 99% of his evolutionary history, or about one million years.

Nutritional studies, and studies on reproduction and fertility, on the selective advantage and establishment of genetic polymorphisms, of unusual and odd alternative ways of employing the central nervous system in its higher cerebral function of language learning and use, computation (number sense and calculation without a numbers system), psychosexual culturally-modified behavior, and cognitive style, are providing data on alternative forms of possible neurological functioning for man of which we would remain unaware, and for moral, ethical, and political reasons be unable to produce or investigate in the clinic or laboratory, once the natural cultural experiments in primitive human population isolates had all finally been amalgamated into the modern civilized cultural veneer which is now imposed upon almost all members of the community of man.

The discovery of new genetic factors, including haptoglobins and hemoglobins, with the elucidation of their biochemical structure and their later use as markers in human population genetic studies, has been a by-produce of these investigations. Similarly, the discovery of immunologically virgin populations, without exposure to respiratory and enteroviruses which are ubiquitous in the civilized world, has permitted 1) fundamental investigation on the immune response in man; 2) investigations possible no where else,

on the persistence of immune response after natural measles infection and live attenuated measles virus immunization, in the absence of circulating virus, yielding data important to the diagnosis and understanding of delayed slow measles encephalitis (subacute sclerosing panencephalitis, SSPE); and, establishing the serological identity of the agent of the 1918-1924 influenza pandemic, to aid in the genetic-historical elucidation of the serial mutations of the influenza virus. By virtue of limited travel during their entire lifetime, and intensive exposure to their natural ecology, members of primitive groups serve as unequaled sentinel populations for revealing the focal microbial agents which can infect man in their environment. Thus, for infections ranging from Chagas disease and toxoplasmosis through arbovirus infections, the primitive groups offer unusually fruitful subjects for investigation.

As a result of our studies on kuru, the first subacute and chronic degenerative disease of the nervous system of man, with a transmission model and with established viral etiology, has been unravelled. We have now inoculated brain tissue obtained either at surgical biopsy or early autopsy from victims of kuru, sporadic and familial types of amyotrophic lateral sclerosis, ALS and the parkinsonism dementia complex on Guam, multiple sclerosis, essential parkinsonism, Schilder's disease, metachromatic leukodystrophy and Dawson's inclusion encephalomyelitis, into chimpanzees and monkeys of several species. In pursuance of this approach, other degenerative diseases previously little suspected to be of possible viral etiology are now under intensive attack. Creutzfeldt-Jakob disease and other forms of spongiform encephalopathy have also been transmitted to the chimpanzee from the brain material of patients. Our SSPE studies and attempts to identify the virus causing chronic encephalitis with focal epilepsy (Kozhevnikov's syndrome, or epilepsy partialis continua), and those causing uveomeningoencephalitis and progressive multifocal leucoencephalopathy, are all an extension of this work. Techniques of explant culture used in the investigation of kuru, with successful isolation of over 80 strains of viruses from long-maintained sterile tissue explants, are now being applied directly and in modified form (trypsinization, and employing cell fusion) to many degenerative central nervous system disorders.

The various laboratory investigations in this project have thus evolved around the theme of elucidating medical problems in the cultures of primitive man by cautiously selecting such problems of immunological, virological, biochemical, and nutritional studies applicable to world-wide use.

Serial No. NDS (CF)-62 OAD 969
1. Collaborative-Field Research
2. Office of Associate Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Slow, Latent, and Temperate Virus Infections of the Central Nervous System of Man and Animals

Sub-Project I: Attempts to isolate transmissible agents from subacute and chronic diseases of the nervous system

Sub-Project II: Conference on measles virus and subacute sclerosing panencephalitis

Sub-Project III: Fluorescent antibody technique in localizing neurotropic virus antigen in whole animals and cell culture

Sub-Project IV: Studies on the ecology, epidemiology and pathogenesis of arbovirus infections

Principal Investigators: D. Carleton Gajdusek, M.D., and Clarence J. Gibbs, Jr., Ph.D.

Other Investigators: Richard F. Marsh, D.V.M., David M. Asher, M.D., Paul Brown, M.D., Stephen Brown, M.D., John J. Hooks, M.S., Richard Sorenson, M.A., Nancy G. Rogers, B.S., and Mint Basnight, B.S.

Technical Assistants: Juliette Harvey, Michael Sulima, Helene Gilbert, Alfred Bacote, Frederick Hess, Paul Martin, Lloyd Horst, Michael Nicholson, Sarah Andersen, and Richard Thomas

Student Assistants: Judith Christianson, Mary Good, Patricia Pearce, Robert Rhorer, Wesley Russell, Diane Thomas, and Stephen Trice

Project Description:

The studies reported in this section are being conducted in the NINDS Laboratory of Slow, Latent, and Temperate Virus Infections at the Patuxent Research Center, Laurel, Maryland, in collaboration with the Bureau of Wildlife and Sports Fisheries, U.S. Department of Interior. Additional associated facilities are with the Laboratory of the Study of Child Growth and Development and Disease Patterns in Primitive Cultures, of which this project is a part. (see Project Report Serial No. NDS (CF)-1282 (I-IX.)

SUB-PROJECT I: Attempts to isolate transmissible agents from sub-acute and chronic diseases of the nervous system

Principal Investigators: Clarence J. Gibbs, Jr., Ph.D., and D. Carleton Gajdusek, M.D.

Other Investigators: Richard F. Marsh, D.V.M., David M. Asher, M.D., Mint Basnight, B.S., Paul Brown, M.D., Stephen Brown, M.D., Francoise Cathala, M.D., Nancy G. Rogers, B.S., and Richard Sorenson, M.A.

Cooperating Investigators: J.D. Mathews and R.W. Hornabrook, Kuru Research Office, Okapa, New Guinea; J.C. Steele, M.D., University of Toronto, Canada; David Poskanzer, M.D., Massachusetts General Hospital, Boston; Richard T. Johnson, M.D., Cleveland Metropolitan Hospital, Cleveland; A.M. Gardashyan, M.D., Mayo Clinic, Rochester, Minnesota; J.T. Sever, M.D., NINDS; J.A. Morris, Ph.D., and Hope E. Hopps, DBS; B.H. Dessel, M.D., Veterans Hospital, Wood, Wisconsin; Elisabeth Beck and Professor P.M. Daniel, Institute of Psychiatry, London; P.A. Palsson, D.V.M., and M. Gudnadottir, M.D., Institute for Experimental Pathology, Keldur, Iceland; C.M. Eklund, M.D., and W. Hadlow, D.V.M., Rocky Mountain Laboratory, NIAID; J. Hourrigan, D.V.M., and H.A. McDaniel, D.V.M., Animal Research Section, USDA; E. Dustman, Ph.D., and C.M. Herman, Sc.D., Patuxent Research Center, Department of Interior; King Engel, M.D., Medical Neurology, NINDS: J.A. Brody, M.D., Epidemiology, NINDS; C. Colson, M.D., Columbia Presbyterian Hospital, New York; R. Katzman, M.D., Yeshiva University, New York; M. Schaeffer, M.D., City of New York Department of Health, and H. Fischman, D.V.M., Otisville, New York; J.N. Freeman, M.D., and Dr. Rome, Stanford University Medical School; G. McKhann, M.D., and Dr. Marino, Grady Memorial Hospital, Emory University, Atlanta; I.H. Pattison, D. Haig, D.V.M., and D. Hunter, Ph.D., ARS, Compton, England; J.T. Stamp, D.V.M., Moredun Institute, Edinburgh; E.J. Field, Medical Research Council, Newcastle-upon-Tyne; M. Kaback, M.D., and S. Palmer, M.D., Department of Pediatrics, Johns Hopkins University Hospital, Baltimore; F. Dixon, M.D., and M. Oldstone, M.D., Scripps Clinic and Research Foundation, La Jolla, California; N. Nathanson, M.D., L. Weiner, M.D., and F. Bang, M.D., School of Public Health, Johns Hopkins University Hospital, Baltimore; W. Zeman, M.D., Indiana University Medical Center, Indianapolis; G. ZuRhein, M.D., University of Wisconsin, Madison; H. Koprowski, M.D., and M. Katz, M.D., Wistar Institute, Philadelphia; I. Kaye, M.D., University of Vermont, Burlington; K. Earle, M.D., and P. Lampert, M.D., Armed Forces Institute of Pathology; P. Van Nuis, M.D., Grand Rapids; T. Rausmussen, M.D., University of Montreal, Canada; W. Greer, D.V.M., and B. Sweet, Ph.D.,

Gulf South Research Institute, Louisiana; C. Espana, Ph.D., L. Schmidt, M.D., and R.E. Stowell, M.D., National Center for Primate Biology, University of California, Davis; A. Lowenthal, M.D., Foundation Born-Bunge for Research, Antwerp

Technical Assistants: Michael Sulima, Alfred Bacote, Helene Gilbert, Mint Basnight, John Hooks, Frederick Hess, Paul Martin, Lloyd Horst, Sarah Andersen, and Richard Thomas

Student Assistants and Part-time Temporary Employees: Judith Christianson, Mary Good, Patricia Pearce, Robert Rhorer, Wesley Russell, Diane Thomas, and Stephen Trice

Project Description:

Objectives: The objectives of this long-term project remain as established in 1962: 1) to attempt to demonstrate infectious etiology for progressive degenerative diseases of the nervous system of man and animals by transmission to experimental hosts and suitable isolation techniques; 2) to determine the epidemiological significance of established prototype strains of viruses that cause slow, latent, temperate and chronic infections of the nervous system of man and animals; 3) to continue to elicit the biological, physical and chemical characteristics of the prototype strains and newly isolated strains of viruses known to induce slow infections, in order to define the basic biology of the new group of infectious and pathogenic microorganisms; 4) to develop new techniques for the successful isolation, identification, and characterization of the etiological agents of degenerative diseases of the nervous system of man and animals; 5) to develop and modify serological techniques to identify newly isolated agents and serve as a marker system in further studies; 6) to prepare, maintain, establish, and explore cell culture lines of autopsied and biopsied tissues from the central nervous system and other organs of man and animals affected with diseases under study, and to apply these techniques to the study of masking, latency, temperateness, persistence, eclipsed, interference, and incompleteness of viruses that cause these slowly progressive degenerative diseases of the nervous system.

Methods Employed: In general, standard and classical techniques for transmission and isolation of viruses are employed with certain notable exceptions; a) the demonstration that the genetic mechanism of the host can determine the host resistance or susceptibility to expression of diseases of interest to our group has required inoculation of specimens into an extensive array of higher primates, i.e., apes and chimpanzees, and a number of species of lower primates, including both old and new world monkeys, as well as domestic animals, i.e., sheep, goats, pigs; and birds--such as ducks, geese, chickens and turkeys--in addition to the entire spectra of ordinary laboratory animals, rabbits, hamsters, guinea pigs, rats, and many genetically defined lines of mice; b) a wide variety of tissue and cell cultures from animal and avian sources, as well as explants of tissue from naturally affected man; c) inoculated animals are held in isolation under carefully controlled observation for a minimum of five years in the case of large animals and up to three years in the case of mice and other small short-lived ani-

mals; d) pre-bleedings and pre CSF's on all animals are tested to determine baseline antibody spectra and serial bleedings and CSF's collected during the course of observation are tested to determine sero-conversion to known agents; in addition, these sera are studied to determine newly formed antigenic properties; e) clinically ill animals are sacrificed with the approval and by recommended procedures of the Animal Care Panel, and serial transmission is attempted by employing the central nervous system and other organs to inoculate the discussed variety of animals; f) detailed neurohistological, as well a general, histological studies are made of each animal that is sacrificed or that has died from nonspecific causes during the study; g) well-established criteria for the selection of cases to be studied, acquisition of central nervous system tissue, preferably at surgical biopsy or at autopsy within a maximum of two hours of death of the patient, and optimal preservation in liquid nitrogen are followed. Major emphasis is also being placed on attempts to determine the nature of "immunopathological" processes contributing to the occurrence of the diseases under study. The following diseases are under study in this laboratory: kuru, Guamanian amyotrophic lateral sclerosis and related Parkinsonism dementia, amyotrophic lateral sclerosis occurring in patients resident in the continental U.S., subacute sclerosing panencephalitis, Schilder's disease, Parkinson's disease, multifocal leucoencephalopathy, metachromatic leucoencephalopathy, multiple sclerosis, progressive supranuclear palsy, necrotizing encephalitis. Additional methods being employed in these studies are concerned with that part of the program devoted to laboratory studies designed to more fully define the nature of scrapie virus as a model virus that causes a slow, but progressive, degeneration of the central nervous system of sheep, goats, and mice. Finally, all inocula are tested for the presence of other microorganisms such as bacteria, rickettsia, PPLO, fungi, and parasites. During the period covered by this report we have conducted serial studies at programmed intervals on chimpanzees, to determine whether there are any changes in hematology, clinical blood chemistries, cerebrospinal fluid values or patterns of electroencephalograms associated with or preceding the onset of the "kuru syndrome".

Major Findings: Kuru: Over 125 chimpanzees, 600 smaller monkeys of 27 species or subspecies, upwards of 105,000 routine laboratory small animals, and 100 each of sheep, goats, and pigs have been inoculated with suspensions of tissues obtained from human patients dying of kuru, Creutzfeldt-Jakob, multiple sclerosis, amyotrophic lateral sclerosis, amyotrophic lateral sclerosis-parkinsons dementia, Alper's disease, Alzheimer's disease, epilepsy partialis continua, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitis, and a wide variety of other human neurological diseases. Particular emphasis has been placed however on those diseases generally grouped as presenile dementias. Significant findings appear below as sub-sections.

Kuru: Suspensions of brain of 10 human patients have induced disease in 14 chimpanzees inoculated either intracerebrally only or intracerebrally and intravenously. Asymptomatic incubation periods have ranged from 16 to 38 months and the duration of clinical disease has ranged from 3 to 11 months. From retransmission studies the kuru virus infectivity is stable for over five years when stored at -70°C and easily passes through a bacterial withholding filter. Thirty-five chimpanzees, and a wide variety of other pri-

mates, have been inoculated with human liver, kidney, spleen, lymph nodes, placenta amnion, milk, blood, serum CSF and urine to determine the pathogenesis of infections. In addition, in an effort to determine the size of the kuru agent other chimpanzees have been injected with human brain suspensions following their filtration through membranes with average pore diameter of 220 mu, 100 mu, and 82 mu. Attempts are also being made to transmit disease through the oral route of inoculation by passing suspensions of brain and visceral tissues through gastric tubes into chimpanzees. These latter experiments may well be associated with long incubation periods. Finally, chimpanzees have been inoculated intracerebrally and peripherally with supernatant fluids obtained from explanted cultures of human tissues that have been maintained in vitro at 35.5°C for over 100 days.

Kuru is serially transmissible in chimpanzees by intracerebral and peripheral routes of inoculation with suspensions of brain or pooled visceral tissues from kuru affected chimpanzees. Kuru is also transmissible from chimpanzees to spider monkeys. Forty chimpanzees have been inoculated in serial passage to elicit physical and biological characteristics of the agent. Ten of 15 animals on second passage and 8 of 13 animals on third passage have developed kuru and have been killed during varying stages of clinical disease. Serial transmission was associated with reduction in incubation period of from 16 to 38 months to 11 to 12 months. Virus is present and neuropathological changes are widespread in the brain as early as 10 months after inoculation in the absence of clinical disease. The virus passes through a 220 nm membrane and has a titer of 10^{-6}IC/0.2 ml. Virus infectivity is not destroyed by exposure to 85°C/30 minutes and undiluted pooled sera from kuru patients failed to neutralize the virus. It is obvious that such high titers of infectious virus as we have demonstrated in tissues in these studies would easily infect human subjects, contaminated as were the Fore children, with the brain and visceral tissues of their kuru-dead relatives during the practice of ritual cannibalism. Such self-inoculations by the subcutaneous route, as well as by conjunctival, nasal and oral routes all undoubtedly occur and could account for the spread of the disease and its maintenance in the population. Experimental studies feeding of kuru infected tissues to chimpanzees have been initiated.

Creutzfeldt-Jakob disease: Transmission of spongiform encephalopathy or Creutzfeldt-Jakob disease, to a chimpanzee inoculated with a suspension of biopsy brain tissue obtained from a patient five months before his death, has prompted attempts at retransmission, serial passage of the disease from chimpanzee to chimpanzee, and further primary transmissions using brain obtained from other patients with the same disease. Chimpanzees have been inoculated intracerebrally and intravenously with brain suspensions from the original patient and from 8 additional patients. Other chimpanzees have received similar inoculations with brain suspensions from the first two animals to develop the disease.

Both retransmission and serial passage from chimpanzee to chimpanzee have been successful. In addition, we have transmitted the disease to two other chimpanzees, each inoculated with a suspension of brain from one of two new patients with spongiform encephalopathy. To date, 5 animals have developed the disease, all 13 to 14 months after inoculation of 0.2 ml ic and 0.3 ml iv of 5% or 10% suspensions of brain. These include 1) A54, the animal of the

first reported transmission from a British patient, 2) A82, the animal inoculated with brain suspension from chimpanzee A54, 3) A79, the animal used for retransmission, inoculated with the same brain tissue which has first caused the disease and which had been stored at -70°C for over two years, and 4 and 5) two animals, A77 and A78, which received brain tissue from two American patients, respectively, taken at autopsy performed soon after death.

The 6 additional chimpanzees still remaining well after inoculation of brain suspension from a different one of 6 further patients with spongiform encephalopathy, were inoculated subsequent to the 5 chimpanzees that have now developed the disease; and only one of these 6 has yet been observed for 13 months, which is the minimum incubation period observed in the 5 animals which have developed the disease.

The 3 patients, each in the sixth decade of life, whose brain tissue have thus far caused similar fatal spongiform encephalopathy in the chimpanzees, have each died from an unremitting and rapidly progressive brain disease with associated severe dementia, disturbances of vision, myoclonic jerks and ataxia. All three were diagnosed as suffering from Creutzfeldt-Jakob disease clinically, and this was confirmed in the first patient by a brain biopsy which showed marked status spongiosis of cortical gray matter. The duration of disease in these three patients was 8, 2½ and 10 months, respectively. At autopsy, neuropathological study revealed the typical pathology of Creutzfeldt-Jakob disease of extensive spongiform encephalopathy of gray matter, neuronal loss, and associated astrogliosis.

The 5 affected chimpanzees, including the second passage animal, have all developed a remarkably similar disease (after incubation periods of 13 to 14 months) in which the major clinical features have been tremor with associated ataxia, myoclonic jerking, fasciculation, somnolence, visual disturbances and dementia. The illness has been rapidly progressive, leading to total incapacitation in about two months. Interestingly, the disease is clearly distinguishable from experimental kuru in the chimpanzee in its clinical aspects, particularly because of the severe dementia, myoclonus, fasciculations and somnolence, none of which are prominent features of experimental kuru. Neuropathologic and electron microscopic examination of the brains of the first two animals that have been killed after developing manifest disease have revealed a vacuolation of the dendritic and axonal processes in neurons and in the astroglial cells, as well as the presence of large rounded neurons containing a pale cytoplasmic inclusion body.

Although the same human and affected chimpanzee brain suspensions that have caused disease in the chimpanzees have been inoculated into several other small laboratory animals, including suckling mice and hamsters, no disease has developed in these animals after over one year of observation. Since kuru has also been successfully transmitted to the spider monkey, this species has also been used for these inoculations. Several primary and stable cell cultures (HEK, BHK21, Vero, WI-38) have failed to reveal any cytopathological effect when inoculated with these brain suspensions.

Subacute sclerosing panencephalitis (SSPE): This is a clinically and pathologically distinct disease of children and adolescents caused by measles virus, as recently proved by viral isolation in several laboratories from brain biopsies. It might now better be called "delayed (and slow) measles encephalitis". Specific CF, HI, FA and neutralization antibody

levels to measles are usually in a hyperimmune range far above the mean titers of late convalescent measles sera tested in our laboratory. In 54 of 72 patients, serum CF and HI antibodies to measles were in this hyperimmune range. CSF had significant measles antibody titers in 47 of 51 patients, although titers were lower than simultaneous serum titers. In a "blind" control study measles CF and HI antibody were measured in 136 sera from 98 patients and 180 CSF from 162 patients of all age groups with a wide variety of CNS diseases. There were 65 serum-CSF pairs from the same patients. In the coded series 49 sera were from 32 patients and 29 CSF's were from 20 patients, with SSPE. Of the 180 CSF specimens the only ones with detectable measles CF antibody were 25 of the 29 specimens from 18 of the 20 SSPE patients. Measles antibody titers in CSF ranged from 1:2 to 1:40 by CF or HI or both. Of the 136 sera studied, 33 of the 49 specimens from 19 of the 33 SSPE patients had measles CF antibody titer of 1:160 or higher; 6 had titers of 1:40 or 1:80, 3 of 1:10 or 1:20, and only 1 was negative at 1:10 (6 were anticomplementary). In contrast, of the 87 sera from non-SSPE patients, only 2 had titers of 1:80, 6 had titers of 1:40-1:80, 22 had titers of 1:10 to 1:20 and 50 were negative at a 1:10 dilution (7 were anticomplimentary). In the two instances where serum titers were 1:80, one was from a patient late in acute measles and the second was from a child with Guillian-Barré syndrome. Serum titers of 1:160 were found only in SSPE patients. Measles antibody estimation on serum and CSF can thus identify most suspected SSPE cases, and confirm diagnosis arrived at from clinical and other laboratory data, obviating the need and risks of brain biopsy. In spite of autopsy confirmation of SSFE, a significant number of brain biopsy specimens from patients with this disease fail to reveal intranuclear (type A) inclusions and are reported as chronic encephalitis of unknown etiology.

Scrapie: Studies to define better the nature of the scrapie virus have been continued and expanded. Major efforts were directed toward eliciting an antigen-antibody system to detect scrapie in affected animals and to measure the immunologic competency of scrapie infected mice. In the first instance, groups of mice inoculated IC with scrapie virus were sacrificed at different time interfals. Sera, brain, spleen and kidney tissues were collected and measured for infectivity as well antigenicity. During terminal stages of clinical disease mice were injected with suspensions of sheep RBC's to measure their immunological responsivenesses. From these studies it was determined that scrapie virus is present in brain and kidney, $10^{-6.0}$ and $10^{-4.5}$/0.03 ml, respectively, from the time of inoculation to the time of deaths 4-5 months later. Although virus is present in the kidneys of mice injected with scrapie titers are of a lower magnitude than brain or spleen and there is a marked prezone phenomena observed in which mice inoculated at 10^{-1} and 10^{-2} survive. These later mice are not immune when subsequently challenged with 500 IPLD50 of mouse brain antigen nor is the asymptomatic incubation period prolonged. Concentrated suspensions of scrapie infected mouse kidney tissues do not neutralize, block or interfere with scrapie virus in mouse brain and mice injected with mized suspensions develop disease and die. Crude and sucrose-acetone extracted brain, kidney and spleen tissues from above failed to fix complement in the presence of serum from naturally infected sheep or goats, experimentally infected mice, hamsters, rats, and hyperimmunized rabbits, chickens or primates. Further, when each

of these sera was tested for the presence of neutralizing antibody employing direct and indirect procedures the results were negative. Mice remain, however, immunologically competent on the humoral level during pre clinical, early clinical and terminal stages of scrapie infection and they respond in a normal fashion to antigenic stimulations. Studies are underway to determine if the cellular immune mechanism remains intact during scrapie infections.

Visna: Visna virus provides an excellent model for the study of multiple sclerosis. The virus produces a demyelinating disease of the white matter of the brains of sheep associated with a long asymptomatic incubation period. The virus has not yet been demonstrated to induce disease in vivo in other than Icelandic sheep; in vitro CPE is produced in cell cultures of sheep choroid plexus, lamb kidney, procine kidney and bovine trachea. Attempts have been made in our laboratory to adapt the virus to primates and mice, rabbits and hamsters. No disease has been observed in any of the inoculated animals either on primary passage or in three subsequent blind passages. The virus does not induce detectable CF, NT or FA antibody response in rabbits hyperimmunized with high multiplicities of visna virus lamb kidney infected cultures. During the period covered by this report tissues were obtained at necropsy from sheep dying from Montana sheep disease, a pneumonitis of sheep in the Western United States. Viral agents were isolated from the brain and lung of two affected sheep, respectively, sera from the two sheep have FA antibody against visna and one sheep has NT antibody against the virus. Attempts are now being made to demonstrate specific visna NT, FA, and CF antibodies against the Montana sheep isolates. Finally, we are attempting to demonstrate the fate of visna at 12 hour intervals following injection of tissue culture adapted virus into mice.

Foamy viruses of chimpanzees: Epidemiology and relationship to experimental kuru: During the course of our studies we have isolated over 100 strains of viruses from explant cultures of tissues of chimpanzees experimentally infected with kuru. Two antigenically distinct viruses, designated Pan 1 and Pan 2, were isolated in primary human embryo kidney cells from explant cultures of brain, spinal cord, sympathetic ganglia, spleen, thymus, kidney, lymph node, and salivary gland tissues from 11 chimpanzees (Pan 1 from 5 and Pan 2 from 6). The viruses produce a vacuolated, foamy, multinucleated syncytia without inclusion bodies in HEK and rabbit kidney cell cultures. Both viruses are ether-, chloroform-, and pH-sensitive and are inactivated by exposure to 56C/30 min. They pass through 220nm Millipore filters but not through 100-nm Millipore-filters. Homologous antibody occurs in the serum of each chimpanzee from whose tissue the virus has been recovered. The viruses are not related to measles, respiratory syncytial, or herpesvirus. Antibodies to one or both viruses are found in chimpanzees not inoculated with experimental kuru; none was found in the sera of kuru patients. Intracytoplasmic vacuolation of neurons and astroglia akin to foamy CPE appears in experimental kuru in chimpanzees and spider monkeys.

Rhesus monkey cytomegalovirus: Persistent asymptomatic viruria: Cytomegalovirus (CMV) has been isolated from the urines of 9 healthy young rhesus monkeys among 11 surveyed. Viruria has been found to persist for over 4 months. The virus was isolated in cultures of human fetal lung fibroblasts (WI-38) in which it produces a cytopathic effect (CPE) similar to that

caused by African green monkey CMV strains. CPE is also produced in fibroblast cultures of human foreskin, of rhesus monkey fetal lung and skin-muscle, and of African green monkey fetal lung and liver origin. Virus has not been demonstrated in the leukocytes of the two infected monkeys tested. Infected monkeys have antibody to rhesus monkey CMV but none to the AD169 strain of human CMV. One infected rhesus monkey, given a single exposure to human CMV strain AD169 by multiple routes of inoculation, developed transient homologous CF antibody which did not persist. A serological survey is now in progress to determine the prevalence of antibody to rhesus monkey CMV in monkeys of several species and the relationship of rhesus monkey CMV strains to those from African green monkeys. This work constitutes the first report of cytomegalo-virus from rhesus monkeys.

Significance: a) The successful transmission of kuru and Creutzfeldt-Jakob diseases with spongiform encephalopathy of gray matter of the brain suggest that these diseases should be included with virus infections which may now be designated the subacute spongiform encephalitides. This group would include kuru, Creutzfeldt-Jakob, scrapie and mink encephalopathy. Further, the spongiform encephalopathies of humans form a group of subacute presenile dementias. Alper's disease, or progressive diffuse cerebral degeneration of infants, and some forms of syringomyelia may possibly also belong to the group. These studies, therefore, are providing new and important findings on the cause and pathogenesis of subacute progressive degenerative diseases of the human brain. They provide optimism in our attempt to transmit multiple sclerosis, ALS and related disease. They have clearly reoriented world-wide investigations in neurovirology.

Proposed course of the project: 1) Identification and characterization of the agent causing disease in chimpanzees; 2) continued long term observation of inoculated animals. Continued serial studies on the fractionation of serum specimens from these animals for the determination of shifts in the electrophoretic patterns, as well as their antibody status which may be indicative of sub-clinical infections; 3) continued effort to develop suitable antigen antibody system for the study of established strains of 'slow' viruses; application of these new techniques to the study of human disease; 4) intensification of the development and application of fluorescent antibody techniques with the model virus and other chronic viruses, such as LCM and rabies, which may remain latent for many years before clinically apparent disease becomes manifest; 5) greater emphasis on growth, cultivation and establishment of cell culture lines of "target organ" nervous tissue from human and animals with degenerative diseases of the nervous system, as well as from cases of "auto-immune" diseases in an effort to isolate an etiological agent in a controlled in vitro environment, detection of abnormal antigenic fractions giving indirect evidence of disease and possible association with known viruses and establishment of new cell lines for the study of viral growth, maturation, and measurement of interferon or interferon-like substances; 6) increased efforts to adapt strains of 'slow' viruses to growth, serial propagation and characterization in tissue and cell culture systems; 7) continued efforts toward the development of procedures for the successful isolation of etiological agents responsible for degenerative diseases of the CNS, such procedures to include cell culture blocking techniques, detection of endosymbiotic relationship of masked, latent, or

temperate viruses and cells in culture and chemotherapeutic lowering of animal resistance to infection; 8) continued efforts to broaden experimental host range for kuru, Creutzfeldt-Jakob, SSPE, visna, and, at the same time, seek out those experimental hosts whose genetic mechanisms render them susceptible to other human diseases under study.

SUB-PROJECT II: Conference on measles virus and subacute sclerosing panencephalitis

Principal Investigators: D. Carleton Gajdusek, M.D., and Clarence J. Gibbs, Jr., Ph.D.

Other Investigators: Michael P. Alpers, M.D., B. Adels, M.D., Nancy G. Rogers, P. Albrecht, M.D. and John J. Hooks

Cooperating Investigators: See: List of Participants and Table of Contents in: Conference on Measles Virus and Subacute Sclerosing Panencephalitis (September 13, 1967). Neurology, 18, Part 2, 1968.

SUB-PROJECT III: Fluorescent antibody technique in localizing neurotropic virus antigen in whole animals and cell

Principal Investigators: D. Carleton Gajdusek, M.D., Clarence J. Gibbs, Jr., Ph.D., and Paul Brown, M.D.

Other Investigators: Nancy G. Rogers, Mint Basnight, Jacob Brody, M.D., Epidemiology, NINDS; Kendall Smith, Ph.D., DBS; David M. Asher, M.D., and Sarah Andersen

Cooperating Investigators: J. Hotchin, M.D., Division of Laboratories, New York Department of Health, Albany; L. Weiner, M.D., Johns Hopkins University, Baltimore

Project Description:

Objectives: Use has been made of lymphocytic choreomeningitis, visna, and measles viruses as models in establishing the methodology to be used in studies of other central nervous system diseases wherein a suspicion of possible virus etiology is entertained. To prepare fluorescent animal antisera to antigens in brain tissue of kuru, amyotrophic lateral sclerosis and other chronic central nervous system degenerative disorders; to purify and concentrate scrapie virus and prepare FA reagents in a search for specific antigens in infected tissues. To elicit and more clearly define measles virus as the etiological agent of subacute sclerosing panencephalitis. To study the pathogenesis of visna virus as a model for multiple sclerosis.

Methods Employed: Lymphocytic choremeningitis and acute neurotropic arboviruses in mice are used as developmental tools in establishing fluorescent antibody techniques in the localization of virus antigen during a slow virus infection involving the central nervous system. Scrapie virus subjected to fluorocarbon deproteinization purification and ultracentrifugation concentration is being studied. A variety of experimental hosts are being immunized with vaccines and serum fractionation procedures are being employed to elicit an immune response.

Major Findings: The demonstration of scrapie antigen fluorescent antibodies using terminal stage sera from diseases mice and sheep in cryostat and parraffin embedded sections has continued to be successful. These studies are, however, being currently supplemented using hyperimmune sera from animals prepared with different purified fractions.

A factor was detected in certain rabbit and guinea pig sera which shows selective affinity for the hypertrophied astrocyte in scrapie-infected mouse brain sections. Its localization is visualized by staining treated sections with a fluorescin-conjugated anti-rabbit or anti-guinea pig gamma globulin. Among many kinds of primary hyperimmune sera tested, only rabbits or guinea pigs immunized with whole human brain tissue showed affinity for "scrapie astrocytes". The factor is heat stable, can be removed by absorbing the serum with human brain homogenate or increasing doses of brain from phylogenetically lower animals.

On the assumption that scrapie may represent a state of immunological unresponsiveness developed perhaps in the course of infection: a) animals were harvested at consecutive time intervals after infection to see whether an immunological conversion from a responsive into an unresponsive, tolerant state develops; b) the antibody-forming system was influenced repeatedly during infection by doses of complete Freund adjuvant followed 24 hours later by X-ray irradiation of a part of the body. Histological examination failed to demonstrate the morphological characteristics of an antigen-antibody reaction typical for neurotropic mice agents. Serological and immunofluorescent evaluation is in progress.

An FA staining technique has been developed for studying visna virus. This allows for a rapid and very sensitive technique for determining the localization of specific visna virus antigen as well as selectively demonstrating specific antibody in sera from a variety of hosts. A pathogenesis study of visna virus in mice and hamsters using the FA technique is underway.

On the assumption that kuru specific antibody does exist in experimentally infected chimpanzees, procedures to elicit an Ag-Ab reaction by FA technique employing conjugated rabbit anti kuru chimpanzee and rabbit anti normal chimpanzee gammaglobulin in a passive immunization study are underway. Initial results show FA staining of positive but not of control specimens and warrant further investigation.

Extensive use has been made of the FA technique employing acridine orange staining of cytomegalovirus in situ in determining the epidemiology of this virus as a latent persistent and chronic infection of rhesus monkeys in our program of slow infections of the nervous system.

The FA technique was employed to demonstrate specific measles viral antibody in the serum and CSF of humans with subacute sclerosing panencephalitis in the blind coded study on sera and CSF from patients with SSPE and a wide

variety of other human CNS diseases. The techniques developed in this laboratory proved to be somewhat more sensitive in measuring the levels of antibody to measles. In some instances it was possible to demonstrate specific FA staining of antigen intracellularly in the biopsy specimens of the CNS of human victims.

Significance and Course: Study of LCM as an example of the slow or latent virus infection and, particularly, as an example of the phenomenon of acquired immune tolerance to infection in the mouse. This work on the pathogenesis of lymphocytic choreomeningitis is used both as a valuable addition to our knowledge in its own right and to establish proceedings which may aid in localizing virus antigen.

Proposed Course: Special attention will be directed toward the study of scrapie and kuru agents in experimental animals. Work on other neurotropic viruses, namely, herpes simplex virus, rabies, mumps, LCM, and some arboviruses is intented in a supporting capacity during elaboration of methodological approaches.

Work will continue on purification of virus material to prepare antigens for immunization and serological procedures (agar precipitation, CFR). The immunization procedure will include long and short-term schedules, using live and killed virus preparations in different stages of purification.

Using labeled immune sera the demonstration of antigen-antibody reaction will be attempted in brain and organ sections from infected animals and in sensitive antigen precipitating tests.

With the possibility in mind that scrapie and kuru may represent infections leading to a state of immunological unresponsiveness (tolerance) or that the infectious agent is for practical purposes non-antigenic, appropriate approaches will be devised for the study of interference phenomena, cytotoxic reactions, presence of acquired transplantation antigens, aided where possible by the FA technique.

Reagents are being prepared which will provide for the screening by FA procedures of all long-maintained explant cultures of human and animal tissues to determine the presence or absence of intra or extracellular viral antigens as an aid to isolation and identification of latent, masked or chronic viruses.

SUB-PROJECT IV: Studies on the ecology, epidemiology and pathogenesis of arbovirus infections

1. Epidemic hemorrhagic fevers
2. Seroepidemiology of arbovirus infections in ecologically isolated primitive indigenous populations:
   a) Seroepidemiology of Alaskan populations
   b) Seroepidemiology of the populations of the Caribbean and Central and South American countries with particular reference to Puerto Rico, Bolivia and Paraguay
   c) Seroepidemiology of Australasian populations
3. Japanese B encephalitis studies on Guam
4. Persistence of arbovirus infections

Principal Investigators: Clarence J. Gibbs, Jr., Ph.D., D. Carleton Gajdusek, M.D., David M. Asher, M.D., Jacob Brody, M.D., and Charles Plank, M.D.

Other Investigators: Edward David, M.D.

Cooperating Investigators: K. Shah, M.D., and F. Bang, M.D., Johns Hopkins University School of Public Health, Baltimore; B.K. Aikert, M.D., Institute of Post-Graduate Medical Research, Calcutta; J. Casals, M.D., Yale University, New Haven, J. Sever, M.D., NINDS; G. Wisseman, M.D., and E. Rosenzweig, Ph.D., Department of Microbiology, University of Maryland; R. Hornabrook, Kuru Research Center, Okapa, New Guinea; F. Schofield, M.D., Public Health College, Gandar, Ethiopia; P. Allen, Ph.D., V. and R. Division, Ft. Detrick; R. Taylor, M.D., University of California School of Public Health, Berkely

Project Description:

Objectives and Methods: a) Japanese B encephalitis on Guam: Work has continued into the epidemiology, ecology and antigenic relationships that exist among the arboviruses in an effort to determine their public health importance and prevalence in selected populations. During the period covered by this report studies were continued in collaboration with the Epidemiology Branch of NINDS designed to determine the neurological sequelae in humans that may have suffered inapparent infections during the perinatal period with Japanese B encephalitis on the island of Guam. b) Persistence of arbovirus infections: Attempts are underway to investigate the mechanisms involved in persistent arbovirus infections of neural and other tissues. The virus Junin (Tacarike group) produced no chronic illness in surviving mice. (Blind passage experiments are planned.) The group B virus Modoc has only recently been found responsible for a case of encephalitis in a child. One strain of this virus has recently been found to produce persistent asymptomatic infections in hamsters. This virus is less dangerous than Junin, and can be studied by tissue culture and plaque techniques and hemagglutination (as well as by mouse inoculation). We are now preparing reagents (seed pools, hemagglutinating antigen and antiserum) for the study of this virus.

Proposed course of the project: Future plans call for completion of the serological survey and detailed neurological examination by resident neurologists. It is proposed that when the present laboratory investigations are completed, these specimens be examined with antigens of other viruses of the ARBO B group. Also, when clinical examinations of those people with significant titers are completed, some conclusions can be made about the neurological sequelae of sub-clinical Japanese B encephalitis infections.

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Serial No. NDS (CF)-65 OAD 1282
1. Collaborative-Field Research
2. Office of Associate Director
3. Bethesda, Maryland

PHS - NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Studies of Child Growth, Development, and Behavior, and Disease Patterns in Primitive Cultures

Sub-Project I: Study of the developmental patterning of the human nervous system (a cybernetics of human development).

a. A research archive for ethnopediatric film investigation of styles in the patterning of the nervous system.

b. Analysis of child care and behavior patterns in primitive cultures from photographic recording (development of techniques and methods).

c. Investigation of non-recurrent phenomena (objectives and selectivity to be used in documentation of aperiodic phenomena to preserve maximum information).

d. Analysis of culturally determined methods of approach to symbolic representation from drawings and art forms of children and adults in primitive societies.

Sub-Project II: Human evolutionary studies in isolate primitive groups.

a. Kuru.

b. Motor neuron disease, and other degenerative diseases in New Guinea and other inbred Pacific Islands populations.

c. Blood group genetic studies in Australasian (Melanesia and Micronesia), and South American indigenous groups.

Sub-Project III: Studies of isolated Micronesian populations.

a. Child development and behavior on Ulithi, Ifalik and Lamotrek atolls and Fais Island.

b. Response to live measles virus vaccine in immunological virgin populations without circulating measles virus (special attention to response in susceptible adults and pregnant women and their offspring).

c. Influenza A2-virgin soil epidemics (epidemiological, clinical, and immunological response and discovery of populations without previous experience with Type A or Type B influenza.

d. Study of infectious disease patterns in remote individual populations.

e. Genetic characterization of the population of the Western Caroline Islands.

Sub-Project IV: Studies of isolated New Guinea populations.

a. Child development and behavior in the Asmat, Tjitjak, Auyu, Kayagar, Western Dani groups of West New Guinea; the Kukukuku (Anga), and Eastern Highland peoples of Papua and New Guinea; and the West Nakanai, Mangsing and Mamusi of New Britain.

b. Infectious disease studies in the diverse, ecologically isolated New Guinea populations.

c. Genetic characterization of New Guinea populations.

d. Hereditary and genetic disease patterns in New Guinea.

e. The Kukukuku: an intensive longitudinal study of growth and development, behavior, disease patterns, human genetics, communication, in an archaic Highland population of New Guinea.

f. Research cinema films on behavior patterns of children in New Guinea.

Sub-Project V: Studies in isolated New Hebrides and Solomon Islands populations.

a. Child development and behavior on Tongariki, the Banks and Torres Islands, and Espiritu Santo.

b. Tongariki: an intensive study of human evolution in the Shepherd Islands.

c. Human genetics and disease patterns survey in the Banks and Torres Islands.

d. Seroepidemiology of infectious diseases in New Hebrides.

Sub-Project VI: Studies on Australian aborigines.

a. Arbovirus seroepidemiologic studies of aboriginal groups in Cape York.

b. Survey of patterns of infectious disease in aboriginal groups in Haast Bluff, Cape York, the Kimberly and Bentnik-Mornington Islands.

Sub-Project VII: Studies of Central and South American Indians.

a. Human genetics and disease patterns of Guayaki and Chaco Indian tribes, and Mennonite colonists in the Chaco of Paraguay.

b. Child growth and development in Guayaki and Ai'yore Indians of Paraguay.

c. Child growth and development in the Aroyo (Moro) Indians of Bolivia and Paraguay.

Sub-Project VIII: Developmental, genetic, and disease patterns in primitive populations of Asia, Africa, and Polynesia.

Sub-Project IX: Experimental developmental neuropediatrics in infantile programming: an empirical approach to the language of information input into the nervous system.

Sub-Project X: Ciphers and notation for the coding of sensory data for neurological information processing:

a. Notational systems for human movement.

b. Ciphers and notation for human form (physiognomy, physique, palm printing, ear form, hair).

c. Theoretical studies in notational problems in mathematics, linguistics, music, dance.

d. Alphabet: a theoretical investigation into their relation to linguistics, and the application to non-linguistic information.

e. Form recognition: neuroanatomic and genetic determination of preferential recognition; and interrelationships of the problem in computer programming and the arts.

Sub-Project XI: Racial distribution and neuroanatomic variations in the structure of the human brain.

Principal Investigator: D. Carleton Gajdusek, M.D.

Other Investigators: E. Richard Sorenson, Clarence J. Gibbs, Jr., Paul W. Brown, M.D., Stephen M. Brown, M.D., David M. Asher, M.D., Michael Alpers, M.D., Vincent Zigas, M.D., Francoise Cathala, M.D., Richard Marsh, DVM, Nancy G. Rogers, Mint Basnight, Helene Gilbert, Michael K. Nicholson, John Hooks.

Project Description:

The Section on Child Growth, Development, and Behavior, and Disease Patterns in Primitive Cultures has continued all projects listed in the Annual Report of 1967-68, with expansion of collaborating investigators, which are reflected in the authorship and studies of publications listed in Publications. The titles of sub-projects and their subdivisions are sufficiently explicit to constitute the project description.

SUB-PROJECT I. Study of the developmental patterning of the human nervous system (a cybernetics of human development).

Principal Investigator : D. Carleton Gajdusek, M.D.

Other Investigators: E. Richard Sorenson, Judith Meyer, Michael Nicholson, Michael Alpers, M.D., Paul Brown, M.D., Stephen Brown, M.D., Vincent Zigas, M.D., Peter Fetchko, Donald Rubinstein.

Cooperating Investigators: Dr. Margaret Mead, Dr. Ted Schwartz, American Museum of Natural History, New York; Alan Lomax, Columbia University, New York; Mr. and Mrs. Mark Jablonko, New York; Dr. Paul Ekman and W.V. Friesen, Langley Porter Neuropsychiatric Institute, San Francisco; Dr. Peter Kundstadter, University of Washington, Department of Anthropology; Kal Muller, University of Arizona, Department of Anthropology; Thomas Kiefer, Dr. Edwin Cook, University of California, Davis; Dr. Gordon MacGregor, American University, Department of Anthropology; Dr. Gordon Gibson, Smithsonian Institution; Dr. Robert MacLennon, Tulane University, New Orleans; Dr. John Hotchin, New York State Department of Health, Albany; Dr. Maurice Godelier, Dr. John Mathews, Dr. Richard Hornabrook, Orneal Kovyers and William H. Bloxam, all of New Guinea.

SUB-PROJECT II. Human evolutionary studies in isolate primitive groups.

Principal Investigator: D. Carleton Gajdusek, M.D.

Other Investigators: Paul Brown, M.D., C.J. Gibbs, Jr., M. Alpers, M.D., F. Cathala, M.D., Stephen Brown, M.D., Nancy Rogers, Mint Basnight, David Asher, M.D.

Cooperating Investigators: Stephen Fazekas, C.S.I.R.O., Sydney, Australia; Eric French, C.S.I.R.O., Melbourne, Australia; Roy T. Simmons, John Graydon, Commonwealth Serum Laboratories, Melbourne, Australia; Cyril C. Curtain, C.S.I.R.O., Sydney, Australia, Vincent Zigas, Public Health Department, Port Moresby, New Guinea.

SUB-PROJECT III. Studies of isolated Micronesian populations.

Principal Investigator: D. Carleton Gajdusek, M.D.

Other Investigators: Paul Brown, M.D., C.J. Gibbs, Jr., J. Anthony Morris, Nancy Rogers, Mint Basnight, David Asher, M.D., Francoise Cathala, M.D., John Hooks, Richard Marsh, Michael Alpers, M.D., Theodore Tsai.

Cooperating Investigators, Jacob Brody, M.D., NINDS:E; Chris Plato, NICHD; Kwang Ming Chen, M.D., Mayo Clinic, Rochester, Minnesota; Stephen Fazekas, M.D., Sydney, Australia; Antonio Golbuu, Yap, Trust Territory of the Pacific; Mr. Jose Torres, Guam Memorial Hospital; Wayne Richards, Ulithi Atoll, Trust Territory of the Pacific

SUB-PROJECT IV. Studies of isolated New Guinea populations.

Principal Investigator: D. Carleton Gajdusek, M.D.

Other Investigators: E. Richard Sorenson, Michael Alpers, M.D., Vincent Zigas, M.D., Paul Brown, M.D., Nancy Rogers, Mint Basnight, Helene Gilbert, Francoise Cathala, M.D., C.J. Gibbs, Jr., David Asher, M.D., Richard Marsh, D.V.M., John Hooks

Cooperating Investigators: C.K. Dresser, M.D., St. Joseph's Hospital, Toronto, Canada; V.F. van Amelsvoort, M.D., Holland; Jan van Baal, Koninklijk Inst. voor de Tropen, Amsterdam; E. Cook, University of California, Davis; Ted Schwartz, U.C.L.A. Department of Anthropology; Dr. Robert MacLennon, Tulane University; John Hotchin, M.D., Albany; Paul Ekman, San Francisco; Roy T. Simmons, J.J. Graydon, C.C. Curtain, Australia; David Kitchin, Columbia University, New York; Alexander Bearn, Rockefeller University, New York; Maurice Godelier, William Bloxam, Richard Hornabrook, John Mathews, New Guinea; Chris Plato, NICHD.

SUB-PROJECT V. Studies in isolated New Hebrides and Solomon Islands populations.

Principal Investigator: D. Carleton Gajdusek, M.D.

Other Investigators: Paul Brown, M.D., C.J. Gibbs, Jr., David Asher, M.D., Nancy Rogers, Mint Basnight, Helene Gilbert

Cooperating Investigators: Robert Kirk, M.D., Australian National University, Department of Genetics, Canberra; Jean Guiart, Sorbonne, France; James MacGregor, M.D., Honiara, British Solomon Islands; Roger Greenough, M.D., William Rees, M.D., Port Vila, New Hebrides

SUB-PROJECT VI. Studies on Australian aborigines.

Principal Investigator: D. Carleton Gajdusek, M.D.

Other Investigators: Michael Alpers, M.D., Nancy Rogers, Mint Basnight

Other Investigators (continued): Helene Gilbert, Paul Brown, M.D., C.J. Gibbs, Jr., Michael Nicholson.

Cooperating Investigators: R.T. Simmons and J.J. Graydon, Commonwealth Serum Laboratories, Melbourne; C.C. Curtain, C.S.I.R.O., Sydney, Australia

SUB-PROJECT VII: Studies of Central and South American Indians.

Principal Investigator: D. Carleton Gajdusek, M.D.

Other Investigators: Stephen Brown, M.D., C.J. Gibbs, Jr., Michael Alpers, M.D.

Cooperating Investigators: W.C. Leyshon, NIDR:HG; Cyril Curtain, Sydney, Australia; J.L. Sever, M.D., NINDS:PR; K. Walls, M.D., Communicable Disease Center, Atlanta; R.L. Anderson, WRAIR; J.A. Morris, DBS:LVR; Arthur G. Steinberg, M.D., Western Reserve University, Cleveland

SUB-PROJECT VIII: Developmental, genetic, and disease patterns in primitive populations of Asia, Africa, and Polynesia.

Principal Investigator: D. Carleton Gajdusek, M.D.

Other Investigators: C.J. Gibbs, Jr., Nancy Rogers, Mint Basnight

Cooperating Investigators: Frank D. Schofield, Kenyatta National Hospital, Nairobi; Peter Kundstadter, University of Washington, Seattle; Thomas Kiefer, University of California; Chris Plato, NICHD

SUB-PROJECT IX: Experimental developmental neuropediatrics in infantile programming: an empirical approach to the language of information input into the nervous system.

Principal Investigator: D. Carleton Gajdusek, M.D.

Other Investigators: E. Richard Sorenson, Michael Nicholson, M. Alpers, M.D.

Cooperating Investigators: Paul Ekman, San Francisco

SUB-PROJECT X: Ciphers and notation for the coding of sensory data for neurological information processing.

Principal Investigator: D. Carleton Gajdusek, M.D.

Other Investigators: E. Richard Sorenson, Michael Alpers, M.D.

Cooperating Investigators: Alan Lomax, Columbia University; Chris Plato, NICHD; Robert L. Kirk, Canberra, Australia; Patricia Hunt, University of California, Berkeley.

SUB-PROJECT XI: Racial Distribution and neuroanatomic variations in the structure of the human brain.

Principal Investigator: D. Carleton Gajdusek, M.D.

Cooperating Investigators: Elisabeth Beck, Peter Daniel, Institute of Psychiatry, London; Paul Yakovlev, M.D., Richard Sidman, M.D. and Dr. Kemper, Warren Anatomic Museum, Harvard University, Boston; Peter Lampert, Kenneth Earle, AFIP, Washington, D.C.; Prof. R. Hassler, H. Stephan, Max-Planck Institute, Neuroanatomic Abteil., Frankfurt, Germany; Dr. A. Hopf, Hirforschunginstitut, Neustadt, Germany.

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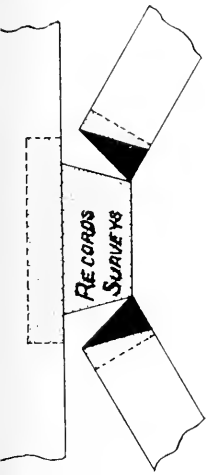

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ANNUAL REPORT
JULY 1, 1968 THROUGH JUNE 30, 1969
EPIDEMIOLOGY BRANCH
COLLABORATIVE AND FIELD RESEARCH
NATIONAL INSTITUTE OF NEUROLOGICAL
DISEASES AND STROKE

Introduction

The major areas of activity of the Epidemiology Branch during the period of this report have been:

I. epidemiologic studies of neurologic diseases;

II. laboratory studies related to the epidemiology of neurologic diseases;

III. the continued activities on Guam and the Trust Territories;

IV. genetic studies of neurologic diseases;

V. activities of the Section on Ophthalmic Field and Developmental Research; and

VI. collaboration, consultation and services rendered to other groups.

The following professional personnel have joined the Epidemiology Branch: Paul Hoffman, M.D. who completed his internship at Grady Memorial Hospital, James Schnur, M.D. who completed his first year of neurology residence at the Massachusetts General Hospital, and Dean Young, M.D. an internal medicine resident from University of Minnesota. George Nemo, Virologist from Catholic University, joined our laboratory as a microbiologist, Jane McNew and Estelle Kornhauser, both R.N.s, and Doris Collie, an ophthalmic assistant, also became members of the Branch.

The following people have left the Branch. Robert Markush, M.D. has transferred to N.I.M.H. to become Chief of their Epidemiology Branch, and J.T. Schwartz, M.D. has transferred to the U.S.P.H.S. Hospital in Baltimore, but plans to return in July, 1969. Richard Goldberg, M.D. has completed his two-year tour of duty, as have Thomas Henson, M.D., Charles Plank, M.D., and Elliot Wilner, M.D. Elaine Lewis, R.N. has transferred to another Branch within the PHS. (Under the Section on Ophthalmic Field and Developmental Research, the personnel changes for that group are repeated.)

The Epidemiology Branch had its most productive and effective year, since my arrival in 1965. This is due to the excellent staff we now enjoy and to the experience which has been gained. We finally moved into Building 36 in March and for the first time laboratories and the rest of the Branch are in one location. Having an active and youthful staff has given the Branch an opportunity to conduct epidemiologic investigations testing specific hypothesis in defined populations which we believe is the most important aspect of our mission. We take the view that chronic disease epidemiology is most efficiently conducted using the "hypothesis testing" approach rather than through large

descriptive population studies. The laboratory now has the full-time services of a virologist, as well as two biologists and with this increase in staff and the new space we are beginning to broaden our interests and increase the depth of our studies. The enlargement of the Section on Genetics in Epidemiology to six members has greatly increased the productivity of that group. Our failure to have a neurologist or a neuropathologist on the Guam projects has limited our opportunities during the past year. We have, however, the first potential break-through in the Guam studies in spite of these limitations as the result of neurochemical studies (see below). Unfortunately, the Section on Ophthalmic Field and Developmental Research was not in full function this year because of the absence of the Section Head. However, the ongoing projects were maintained and the tempo will undoubtedly increase again with Dr. Schwartz' return.

I. Epidemiologic studies of neurologic diseases

Multiple Sclerosis

We have made perhaps a critical observation concerning the antibody titers to mumps and measles among multiple sclerosis patients and controls. Previous studies have indicated that antibody titer to measles among multiple sclerosis patients is higher than among control groups. From our studies it appears that antibody levels in the serum of MS patients is higher for measles and mumps than for most control groups. The antibody levels were not higher, however, among uneffected siblings of MS patients born within 3 years of the patient. High measles antibody and high mumps antibody were not necessarily found in the same individuals indicating that the reason MS patients and their siblings had higher titers than other control groups was not because of shared antigens between these two paramyxoviruses. If our conclusions are substantiated, there are several possible explanations. Among them are that the families of MS patients have a basic immunologic defect; that there were dual infections in MS families during the myxovirus infection and the combined viral infections altered the normal immune response; or that these families were exposed to a different virus than were the controls.

Our laboratory tests continue to support our original finding that the lymphocytes of multiple sclerosis patients are not unusually sensitive to cerebrospinal fluid and in addition, do not appear to be sensitive to a series of other virus antigens and brain products.

Amyotrophic Lateral Sclerosis (stateside studies)

Neuropathologic studies of veterans who served on Guam and, subsequently, died of ALS have demonstrated neurofibrillary tangles which are seen in the ALS cases encountered among Chamorros. In addition, preliminary analysis of 12,000 statesiders who worked on Guam for more than one year between 1945 and 1955 reveals that these individuals have not suffered from an unusually high rate of ALS. The implication of these studies is that adult statesiders exposed to the Guam environment do not develop ALS. This could either be due to the fact that the incubation

period for any environmental factor (toxic, viral, etc.) is too long or occurred too late in life to cause ALS among these statesiders or that the Guamanians have a genetic susceptibility to this disease.

Epidemiologic studies of ALS using hospitals and state health records in North Carolina and data from the Social Security Administration suggest that ALS death reporting is of questionable value. In patients in whom ALS was diagnosed at neurologic referral centers only 80% of those who died had ALS as the principal or underlying cause of death. There is a further suggestion from these studies that either the patterns of ALS are shifting to involve older individuals with a more protracted course of disease or that there is a considerable amount of misdiagnosis even at highly regarded neurologic diagnostic centers.

We are conducting epidemiologic studies of the suggested relationship between pancreatic insufficiency and ALS. To date our studies of individuals in whom surgery for peptic ulcers was performed (thus creating a malabsorption syndrome similar to that observed in pancreatic insufficiency) do not develop ALS. We are finding, however, that malabsorption does cause considerable neurologic disability and in our preliminary analysis, at least 25% of people with malabsorption syndromes have clear neurologic deficits. Controls for these studies include individuals with peptic ulcers who were treated by vagotomy and thus have normal utilization of pancreatic enzymes. These patients are being examined currently and results are not yet available.

Hereditary Spino-Cerebellar Degeneration

We are studying an unusual form of hereditary spino-cerebellar degeneration in a large kindred with onset very late in life, frequently in the seventh or eighth decades. These syndromes usually appear in childhood. We are also compiling data on other kindreds with more typical spino-cerebellar degeneration and related syndromes such as familial ALS.

Drug-induced Parkinsonism

Our studies of drug-induced extrapyramidal disease have revealed that there are at least two symptom patterns occurring among the patients implying that the usual designation of "drug-induced parkinsonism" is over simplified and a bit misleading. We find that one group of patients has parkinsonism-like features and another group has lingual-oral-facial dyskinesia with or without limb chorea. These symptoms are associated primarily with phenothiazine ingestion. We have encountered them, however, in patients in whom these drugs were not used.

It is stated in the literature that Parkinson's disease is less common among negroes. Our studies of drug-induced extrapyramidal disease have revealed that the rate of appearance of these symptoms is approximately the same among whites and negroes.

In collaboration with others we have preliminary evidence which indicates that L-dopa is not effective against phenothiazine-induced parkinsonism. Biochemical studies also suggest that the metabolic pathways in the drug-induced disease are not the same as in paralysis agitans.

Unilateral Parkinson's Disease

We tested the hypothesis that surgery in unilateral Parkinson's disease could alter the natural progress of the disease and delay or prevent symptoms from appearing on the contra-lateral side. Using five-year follow-up examinations on patients and controls we found that surgery does not alter the rate of progression of the disease to the opposite side. We found, however, that in a small number of cases with unilateral parkinsonism, the surgery provided a complete cure of the disease. By analyzing our data in this study and reviewing several other series of parkinsonism patients we have achieved a better understanding of the natural history of unilateral parkinsonism. It appears that there is a benign form usually occurring among patients whose disease onset is early in life and associated either with encephalitis or coma. A certain percentage of this group has permanent or very slowly progressive tremor and rigidity essentially confined to one side of the body. It is in these individuals that complete cures are possible by surgery.

Relationship Between Astrocytoma and Toxoplasmosis

We have completed the initial phase of a study of toxoplasmosis antibody in astrocytoma patients which we initiated as the result of a report of a higher incidence of toxoplasmosis antibody among these patients. We did not encounter an unusually high proportion of positives among the astrocytoma patients, but we did find several extremely high titers. At present, we do not understand the significance of these observations and are evaluating the patients with high titers to determine if neuropathologically, or from other aspects, they differ from the rest of the group.

Strokes and the Oral Contraceptive Pill

Our studies of the relationship between cardiovascular disease and consumption of the contraceptive pill supports other evidence that certain venous conditions such as phlebothrombitis and pulmonary embolism do occur more frequently among pill-takers, but that strokes and other arteriovascular problems are not related to pill ingestion.

II. Laboratory studies related to the epidemiology of neurologic diseases

We have utilized our methods for freezing lymphocytes to expand our studies of multiple sclerosis and other neurologic diseases. We are still unable to confirm earlier reports that multiple sclerosis patients' lymphocytes are sensitive to any normal CNS products or to a series of viruses or extracted

brain antigens. We are developing new and simplified techniques for measuring lymphocyte transformation which will enable us to broaden our work considerably. At present, we have had some success using spectrophotomotry of protein or RNA or DNA as the end point. A series of studies are in progress to determine whether steroids affect lymphocyte response and whether after a stroke with the sudden release of large amounts of potentially antigenic brain material into circulation there is an auto-immune response detectable by lymphocyte transformation.

III. The continued activities on Guam and the Trust Territories

We continued to follow the large case-load of amyotrophic lateral sclerosis (ALS) and parkinsonism dementia (PD) patients on Guam (for details, see my trip report of Mar. 11, 1969). There is no evidence of a decline in incidence of ALS or PD. Other neurologic diseases which we study on Guam also appear to be occurring in approximately the same patterns as previously. Our most important recent finding was the documentation of major metabolic defects in dopamine and perhaps, in serotonin metabolism among PD patients of Guam. These abnormalities are consistent among PD patients and apparently occur among ALS patients and occasionally among controls. This observation parallels the finding that neurofibrillary changes occur in ALS patients and controls and possibly signals a basic defect among Chamorros which predisposes to these conditions. We have made arrangements to secure pathologic specimens from ALS patients on the Philippines, since cases of ALS among Filipinos have been seen on Guam and in one, the neuropathologic features of Guamanian patients (neurofibrillary changes, etc. were present). Lacking our own neuropathologic competance curtails our effectiveness in these studies and more particularly in the vital study of the brains of control Guamanians who did not have ALS or PD, but whose brains contain neurofibrillary changes.

Genetic studies on Guam of the offspring of the first 100 ALS and PD deaths with matched controls has revealed a tendency for family aggregation. This does not, of course, imply a single genetic factor, since the aggregation could be the result of environmental factors. The offspring of patients will be followed for the next several years during which time many will enter the age of susceptibility, so that numbers will become sufficient to give more definitive insights as to the relative importance of genetics and environment.

We continued to study other neurologic diseases on Guam and the Trust Territories. Our extensive survey of inborn errors of metabolism has failed to uncover any unusual diseases in these areas. Studies of epilepsy continue to reveal an unusually high rate of febrile convulsions and also true epilepsy on Guam. This investigation is intended to serve both as a model for epidemiologic studies of epilepsy in tropical island populations and to provide data on the rate of epilepsy among Guamanians. In California we continue to find ALS patients among the Chamorros who migrated there, but it is notable that we have yet to encounter patients with parkinsonism-dementia of Guam. During the period of observation we would have expected to have found at least one or two in California. The implication is that the precipitating factor for parkinsonism-dementia exists on Guam and apparently not in California.

Our contract with the University of California to study cerebrovascular and attendant metabolic abnormalities has revealed a remarkably high incidence of hyperuricemia and hyperglycemia in Chamorro populations on Guam, Rota, and California. The patterns of disease related to these metabolic abnormalities are being analyzed now. It is apparent that Chamorros have a notable excess of chemical gout and diabetes and that stroke and hypertension are occurring at elevated rates. Further understanding of these observations could lead to the illucidation of specific factors which precipitate cerebrovascular disease. The islands of the Pacific offer remarkable and unique opportunities to study genetically homogeneous populations living under different conditions of diet and stress which permit detailed analysis of the causative features of these conditions.

During this year we documented a fascinating genetic eye disease among the people of the island of Pingelap among whom approximately 10 percent are born blind. The disease is a form of retinitis-pigmentosa and is apparently inherited as a recessive trait. The group of disease with retinitis-pigmentosa in which there is a genetic component is poorly understood in medicine and having access to a pure genetic isolate will undoubtedly add much to the understanding of these conditions. Epidemiologic observations suggest that in addition to a genetic factor there may be an environmental component involved in the pathogenesis of this form of blindness.

IV. Genetic studies of neurologic diseases

Activities of the Section on Genetics in Epidemiology during its second year centered in two areas: clinical and biochemical studies of movement disorders, particularly torsion dystonia (TD); and genetic and clinical evaluation of familial acoustic neuroma.

Movement disorders: Our study of more than 100 families has demonstrated at least two hereditary forms of TD: a recessive type with early onset and rapid course which is unusually frequent in that portion of Jewish populations having central and eastern European ancestry, and a dominant form which is more variable in its age at onset and course and which has been reported sporadically in many populations.

Biochemical studies in this group of disorders are underway in the laboratories of two collaborators, Dr. Mary Bazelon, Assistant Director of the Neurologic Research Ward at Children's Hospital, Washington, D.C., and Dr. Thomas Chase, Chief, Unit on Neurology, NIMH. Initial results on four patients point to abnormalities predicted in the catecholamine-serotonin systems. On the basis of this information treatment has been tried using L-dopa. Two patients with recessive TD have shown possible improvement, but the duration of treatment is too short to evaluate the response. A third patient with the dominant form is also receiving L-dopa with slight improvement. The fourth patient cannot be classified definitely as to the type of torsion dystonia and he has not yet responded to treatment. We do not regard L-dopa as specific therapy for TD, but have explored its use because preliminary data

suggest that a biochemical defect of biogenic amine metabolism may cause TD. We are hopeful, however, that through these studies we may pinpoint the specific gene defect and biochemical abnormality in each form which could lead to effective therapy.

A startling and potentially most significant event has been the preliminary finding that those with recessive TD have a significantly higher IQ than do a nonaffected control group who are matched for age, sex, ethnic and social background. Data on the first six patients and six controls indicate individual IQ scores in the patient group range from 111 to 170 with a mean of 131 and standard deviation of 17.3 while controls have scores ranging from 92 to 127 with a mean of 113 and standard deviation of 13.8. The difference between mean IQs for these two groups is significant at the level of P = .04. We now have expanded this initial group to a total of 76 individuals with the same general trend persisting. We may well be faced with the fascinating, but fearsome prospect of having demonstrated a gene associated with increased intellect with the implication that if we discovered the biochemical mediation of this gene we could influence intellect.

We are expanding our series so that these critical observations can be more adequately documented. We hope to have information on all appropriate patients in the United States. In addition, a simple step which should give us highly useful information, and which we have proposed each of the last two years, would be to look at the 27 patients in Israel with torsion dystonia who have been reported to us. This group would be especially valuable to study from a psychometric standpoint, since bias in socioeconomic status inherent in looking at second and third generation American Jewish families would be avoided. A genetic field worker, neurologist and psychologist are available in Israel and simply await our presence to proceed.

Other studies underway in the area of movement disorders include the exploration of the relationship of dystonia to torticollis, Parkinson's disease and familial tremor. The role of hereditary factors in each of these conditions is being explored through patient material obtained from numerous medical centers as well as the NAS-NRC Veterans Administration twin registry.

A study of 1800 Guamanian migrants living in California designed to evaluate genetic or environmental factors in amyotrophic lateral sclerosis and parkinsonism-dementia (PD) as they appear on Guam has been completed and is due to be published in the journal, Neurology. Two cases of ALS were found in this population indicating the frequency of this disease is similar in the migrant group to that on Guam and suggesting a genetic factor and/or early exposure to an environmental factor is responsible for each disease. Two suspect cases of PD were also observed, but since they are atypical their significance is not clear.

Familial Acoustic Neuroma: Restudy of the kindred originally reported by Gardner and Frazier in 1930 has been largely completed from the genetic standpoint. Useful information is now available on at least 1100 members of the family; 110 are considered definite or probable cases. Clinical characteristics include: an average age at onset of 19 years; survival after onset of symptoms in unoperated cases of 19 years with range

of 2 to 44 years; initial symptoms of deafness in 52 percent, tinnitus in 33 percent, imbalance in 10 percent and facial twitching in 5 percent; earliest signs are decrease or absence in caloric response and/or diminished air or bone conduction. Surgery as performed in the past has not been helpful. The trait is autosomal dominant with virtual complete penetrance and appears to be distinct from classical neurofibromatosis. Detailed out-patient examinations have been carried out in collaboration with the Departments of Otolaryngology and Radiology at Johns Hopkins Hospital. These results indicate that no single test can be relied upon for early diagnosis of these tumors. Brain scan is a useful addition to the diagnostic work-up.

In the future interested departments at Johns Hopkins Hospital will continue detailed clinical and physiological studies in this family while the Genetics Section will assume a largely advisory role.

Other studies: A report dealing with hearing loss and otitis media on Guam where the rate of hearing loss is 3 to 4 times that seen in the United States has been submitted for publication.

Programs which are contemplated in the near future or have recently been initiated include the following: the genetics of dizygotic twinning; clinical and genetic studies of myoclonic epilepsy; survey of Micronesia for rare genetic traits, since this area provides an ideal hunting ground for recessive disorders resulting from inbreeding.

V. The expanded activities of the Section on Ophthalmic Field and Developmental Research

Personnel

During the past year, the professional staff of the Section comprised Dr. Frank H. Reuling, Acting Head, and Mrs. Doris Collie, Ophthalmic Technician. Mr. Mark Wilburn, engineer, came on active duty in July for full time assignment with the Medical Systems Laboratory of the National Center for Health Services Research and Development. Dr. J.T. Schwartz left the Section in July for a one-year clinical assignment with the Division of Direct Health Services at the U.S.P.H.S. Hospital in Baltimore. While away from the Institute, Dr. Schwartz has continued to supervise the activity of the Twin Registry for Eye Examinations.

Twin Registry for Eye Examinations

A. Heritability of the effect of corticosteroids on intraocular pressure.

Major emphasis during the past year centered on the study of the heritability of the effect of corticosteroids on intraocular pressure. This investigation is designed to contribute to the examination of a popular hypothesis that the ocular hypertensive response to topical steroids is transmitted by means of a simple autosomal genetic mechanism. This hypothesis

bears directly upon the current concept of the etiology of chronic simple glaucoma. If inheritance is found to play a major role in the transmission of the steroid response, this research would offer strong support for the need for further studies to define thoroughly the relationship between steroid responsiveness and chronic simple glaucoma. If inheritance is found not to play a significant role, the evidence would suggest a need to re-examine the popular basic hypothesis of autosomal inheritance of the steroid response. Over 45 pairs of twins have participated in the complete course of steroid testing during the past year.

B. Expansion of the local register.

During the past year we have continued to locate and examine additional pairs of twins residing in the Washington Metropolitan area. These preliminary examinations provide an opportunity to:

1. Obtain base-line measurements to identify and enumerate ocular abnormalities among members of the twin registry as an aid in selection of sub-sets for future investigations.

2. Obtain data for direct estimates of heritability. Descriptive data which will be analyzed will include anthropometric measurements, blood groupings, fundus characteristics, iris stromal patterns and ocular dominance.

3. Offer a careful examination and exchange of information for the benefit of the twins and thereby encourage their informed interest in participating in proposed detailed investigation.

We now have in the local registry somewhat over 600 pairs of twins.

C. Factors which influence the progression of myopia.

Bifocal lenses, undercorrection, contact lenses and the use of cycloplegic drugs are among treatments used by practioners in an effort to control the progression of myopia. The efficacy of such treatment is unsettled. The study of young identical cotwins who are similarly myopic offers a unique approach to this question. Through our screening examinations we have begun to assemble this study population and preparations for a protocol development are in progress. This will be a prospective case-control study, wherein one member of each twinship will be offered "therapeutic" treatment while the cotwin receives standard refraction correction.

D. Collaborative Investigations.

During the past year we were able to begin our first twin investigations through collaboration with other institutes. These include

a study of genetic factors in cardiovascular diseases being undertaken by the Field Epidemiologic Research Section of the NIH, a study of fetal loss associated with Xg^a blood type incompatibility between mother and offspring, undertaken in collaboration with the Children's Diagnostic and Study Branch of NICHHD and a study of the heritability of blood lipid characteristics being undertaken by the Molecular Disease Branch, NIH. Project Reports for these investigations will appear in the Annual Reports of the appropriate institutes.

E. Expansion of the twin register within PHS.

In the past we completed an agreement with the Division of Direct Health Services, U.S.P.H.S., which provides the opportunity to undertake twin examinations in cooperation with U.S.P.H.S. Hospital facilities. Efforts to begin our first examination center (Baltimore, Maryland) within the framework of this agreement were curtailed during the year due to limitations of funds and secretarial positions. During the past year we were successful in negotiating for permission to examine twin members of the NAS, NRC register who reside in the Baltimore metropolitan area. Since examinations of these twins will be required for the steroid investigation, continued efforts will be made to acquire the resources to pursue this necessary collaboration with U.S.P.H.S. Hospital, Baltimore, Maryland.

Television Ophthalmoscopy

The television ophthalmoscope is of interest to this Section because of its potential value as a population screening device and also because of the need for collaborative effort in its further development. Last year we entered into an agreement with the Medical Systems Development Laboratory of the National Center for Health Services and Research Development to undertake an analysis of the relative merits and project costs of specific applications of television ophthalmoscopy. They have prepared a development plan and are proceeding with its implementation by direct operation and outside contractual agreements. A critical evaluation of the quality of signals which can be derived for selected clinical applcations is the objective of the current phase of the development. Clinical trials for data acquisition and preliminary programming for automatic processing of the electronic signals will follow.

Malignant neoplasms of the eye

Pertinent data have been extracted from 1,108 death certificates in which the primary cause of death was assigned to Rubric 192 (malignant neoplasms of the eye) during the years 1959-1961. Statistical tables have been completed based on statistical information classified according to probable histologic diagnosis. A report in preparation will provide the first description of the U.S. mortality experience with specific ocular

neoplasms based on the interpretation of death certificate information. This report will be completed when Dr. Schwartz returns to the Section next year.

Influence of synthetically derived aglycone of cycasin on ocular tissue

This study has been continued in collaboration with the Laboratory of Experimental Pathology, NIAMD. Intracameral injection of rabbits using known oncogenic agent (hydroxyazoxymethane) have been completed in the past and the appearance of the ocular fundus has been followed over the past year. There has been no evidence of neoplasia or other progressive intraocular change. The period of observation will be continued.

VI. Collaboration consultation and services rendered to other groups

During the year the Chief of the Epidemiology Branch has served as Program Chairman of the Epidemiology Section of the APHA, Vice President of the Muscular Dystrophy Association, a member of the National Multiple Sclerosis Medical Advisory Board, and a member of the National Multiple Sclerosis Advisory Committee on Research in the Etiology, Diagnosis, Natural History, Prevention and Therapy of Multiple Sclerosis, a member of the Commission of Geographic Neurology, World Federation of Neurology, a member of the APHA Program Area Committee on Communicable Diseases, and a consultant to the project - Amyotrophic lateral sclerosis in the Kii Peninsula, Japan, and to the Encephalitis Conference at the Institute of Neurological Sciences, Pacific Medical Center, San Francisco, California.

Our group has maintained active collaboration with other groups in NIH. Within NINDS, Dr. Gadjusek and Dr. Gibbs continue to receive our ALS and PD material and also other pathologic material such as Crutzfield Jacob disease for innoculation into primates and other laboratory hosts. We are working with Dr. Sever on a series of serologic studies involving multiple sclerosis, toxoplasmosis, and sub-acute sclerosing panencephalitis. We also collaborate with Dr. Thomas Chase, NIMH, on a series of studies of amine metabolisms in diseases of the extrapyramidal system. We are working with numerous organizationa outside of NIH including the Department of Genetics, School of Medicine, University of Hawaii, the Department of Otolaryngology at Johns Hopkins, the Department of Pathology at Massachusetts General Hospital, the Armed Forces Institute of Pathology, the National Research Council Follow-up Agency, several medical schools in North Carolina, and the Mayo Clinic.

In addition, see the following Contract Reports.

CONTRACT NARRATIVE
Epidemiology Branch, C&FR, NINDS
Fiscal Year 1969

THE NATIONAL ACADEMY OF SCIENCES (PH43-64-44)

Title: The Epidemiology of Stroke

Contractor's Project Director: Dean M. Nefzger
Roy Acheson, M.D.
Albert Heyman, M.D.

Current Annual Level: $64,400.00

Objectives: The contractor will: (a) Analyze death certificates of all veterans dying in 1967 in Georgia (high mortality area) and five Rocky Mountain States (low mortality area). From the certificates approximately 1,000 certified CVA deaths in each area and 100 randomly selected controls will be chosen for further analysis (2,200 cases total). From these basic data, the frequency of reported CVA among veterans will be compared with male populations in similar areas to determine if the geographic variations reported for civilians occur among veterans; (b) By review of available hospital records and when necessary by physician or family interview, the validity of the diagnosis will be established in order to estimate the relative frequency of mistaken diagnosis or failure to make the diagnosis of CVA; (c) By review of the accumulated information on veterans dying of CVA an estimate of the relative frequency of specific types of CVA will be compiled; (d) All verified stroke deaths and all errors in death certification will be analyzed in terms of geography, age, race, place of residence, marital status, from the point of view of sources of information (competance of certifying individual) and other variables; (e) During this investigation the complete Military and Veterans Administration folders will be reviewed for a subgroup of 50 cases and controls per state in order to evaluate the usefulness of these records in subsequent studies. In addition, all other avenues of ascertainment of a valid rate of CVA among veterans will be explored in order that a definitive study of veterans population be conducted in the future when the great bulk of veterans of the Second World War arrive at the age of high risk for CVA.

Major findings: A total of approximately 1,000 stroke deaths and 2,800 deaths from other causes have been compiled. The data on these cases are ready for final analysis. A preliminary review of the stroke cases in Georgia which has a high mortality rate from stroke versus the rocky mountain states which have a low reported mortality from strokes has revealed surprising and potentially important information. It appears that this wide discrepancy may be purely artifactual and the result of different reporting habits by physicians in the two areas. It is uncommon for stroke to be listed as underlying cause of death in the rocky mountain states. This finding is at variance with the Johns Hopkins University Epidemiology of Stroke study which we supported by contract (PH43-66-920).

Significance to NINDS Program and Biomedical Research: The epidemiological patterns of stroke are poorly understood, although it is suspected that there are regional differences throughout the U.S. Any information confirming these differences and indicating a cause for these differences could lead to a better understanding of causation and prevention in this important cause of morbidity and mortality.

Proposed Course of Project: The project has been extended for another year with the intention of subsequent extension for at least one more year.

CONTRACT NARRATIVE
Epidemiology Branch, C&FR, NINDS
Fiscal Year 1969

THE JOHNS HOPKINS UNIVERSITY (PH43-67-1347)

Title: The Epidemiology of Parkinson's Disease

Contractor's Project Director: Abraham M. Lilienfeld, M.D.
Irving I. Kessler, M.D.

Current Annual Level: $54,324.00

Objectives: The contractor will: (a) Select a group of hospitals to provide sufficiently large groups of patients with Parkinson's disease; (b) Assemble groups of patients with parkinsonism, Parkinson's disease and similar neurological deficits who have been hospitalized for any reason or seen in any hospital clinic; (c) Assemble matching groups of patients without parkinsonism symptoms who have been hospitalized at the same institutions and who are similar to the cases in age, sex, race, and other pertinent demographic characteristics; (d) Select a probability sample of physicians (neurologists, general practitioners, general surgeons, and internal medicine practitioners) and from them secure a cohort of patients with parkinsonian symptoms who have not been hospitalized; (e) Compare the patients and their matched controls with regard to epidemiologic characteristics of possible relevance to the incidence of or morbidity from Parkinson's disease, including familial mortality experience and smoking histories; (f) compare, within the patient groups, the epidemiologic characteristics of those with specific parkinsonian symptom complexes; (g) Compare the hospitalized and nonhospitalized parkinsonian patients in order to test whether there are methodologic biases in studies restricted to hospitalized patients; (h) Assemble a large group of patients known to have had Parkinson's disease, parkinsonism or similar neurological deficits as the basis for an analysis of the overall and cause specific mortality of the decedents; (i) Reach conclusions as to the adaptability of the case-control method to the study of Parkinson's disease; and (j) To the extent that the case-control method proves to be inadequate, design other more suitable methods for the epidemiological study of Parkinson's disease.

Major Findings: During the time from the awarding of the contract to the present writing the study has been concerned with accumulation of patient and control data. No analysis has been attempted as yet.

Significance to NINDB Program and Biomedical Research: At present understanding of risk factors and natural history in parkinsonism is limited to a few studies primarily in clinic populations. The extension using a case-control matching could provide important information for this extremely important neurologic condition.

Proposed Course of Project: The project will run for two years. At present, however, the first year accumulation of work demands that additional time be devoted to tabulating and documenting the cases and controls. Therefore, the first year of the project was extended until September 1968 without additional funds. At that time the second year of the project will commence should funds be available.

CONTRACT NARRATIVE
Epidemiology Branch, C&FR, NINDS
Fiscal Year 1969

THE UNIVERSITY OF CALIFORNIA-BERKELEY (PH43-68-36)

Title: Health Survey of Stateside Guamanians

Contractor's Project Director: Reuel Stallones, M.D.
Dwayne M. Reed, M.D.

Current Annual Level: $179.000.00

Objectives: The contractor will: (a) Analyze mortality experience of Guamanian residents of California for the past ten years in comparison of that of California residents generally; (b) Contact adult Guamanians residing in California and enlist the voluntary participation in the survey of approximately 1,000 subjects; (c) Secure family and individual health histories from recruited subjects, and administer a screening examination comprised of: neurologic examination, psychological examination to test for dementia and motivational aspects, EKG, BP, blood tests for cholesterol, triglycerides, uric acid, and glucose; (d) Conduct similar examinations of a matched group of Guamanians residing on Rota Island, Saipan Island, and Guam; (e) Code and process data gathered and analyze results, demonstrating whether or not disease patterns vary between Guamanian residents in the U.S. and the general population, and between Guamanian residents in the U.S. and Guamanian residents in the Pacific.

Major findings: The investigators documented an unusually high rate of hyperuricemia and hyperglycemia among Chamorros living on Guam, in California, or on Rota. The patterns of diabetes and gout differed to some extent, although the final analysis of these data are not completed. Most impressive were differences in cholesterol levels, tri-glycerides and hypertension in the various populations. Although analysis is not final it appears that hypertension is unusually common on Guam and in certain other islands of the Trust Territories is virtually absent.

Significance to NINDS Program and Biomedical Research: Establishing a baseline on Guam for metabolic disease and cardiovascular disease as well as some knowledge of psychological patterns and patterns of neurological disease will be invaluable to our studies on Guam. They will also provide important information concerning patterns of disease among migrating populations.

Proposed Course of Project: The project will run for one more year at which time the results will be analyzed and the necessity for further studies will be determined.

CONTRACT NARRATIVE
Epidemiology Branch, C&FR, NINDS
Fiscal Year 1969

THE MASSACHUSETTS GENERAL HOSPITAL (43-68-982)

Title: Screening of Blood and Urine for Abnormal Amino Acid Patterns

Contractor's Project Director: Vivian E. Shih, M.D.

Current Annual Level: $12,060.00

Objectives: The contractor will perform cromatographic screening of approximately 1,000 sample, each of blood and urine for detection of disorders of amino acid metabolism among residents of Guam and the Trust Territories. Testing will be performed by routine methods developed and utilized in the contractor's laboratory conducting repeat screening on tests of blood or urine samples as needed in order to confirm or nullify the significance of unusual patterns.

Major findings: To date, the blood and urine of approximately 500 Guamanians or residents of other islands of the Trust Territories have been screened for inborn errors of metabolism. At present, there are no apparent concentrations of inborn errors of metabolism in Guam and on other island populations and surprisingly few abnormalities have been encountered. It is hoped that before this study terminates we will establish certain unusual patterns in the isolated and potentially inbred populations which we are studying.

Significance to NINDS program and biomedical research: As the study continues on Guam we become more convinced that metabolic diseases play an important role in causing amyotrophic lateral sclerosis and parkinsonism dementia. In addition, on many islands in the Trust Territories we notice abnormal genetic patterns of disease which suggest that certain inborn errors of metabolism may exist. Should we identify these specific metabolic errors on Guam or in the other islands we may gain important insights into the cause of the neurologic diseases in Guam and by using population isolates gain information concerning metabolic pathways in a given population which would provide information on metabolic processes in human populations anywhere.

Proposed course of project: Will terminate in September, 1969.

Serial No. NDS (CF) - 55 E 201
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Studies on amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam (ALS-PD)

Previous Serial Number: Same

Principal Investigators: Jacob A. Brody, M.D.
Edward W. Brink, M.D.
NINDB Research Center

Other Investigators: Jose Torres
NINDB Research Center
Francisco Leon Guerrero
NINDB Research Center
Manuel T. Cruz
NINDB Research Center
Roswell Eldridge, M.D.

Cooperating Units: NINDB Research Center, Agana, Guam
Special Chronic Disease Studies, C&FR, NINDB
Laboratory of Slow, Latent, and Temporate Viruses, C&FR, NINDB
Department of Epidemiology, School of Public Health University of California, Berkeley
Mayo Clinic, Rochester, Minnesota
Department of Pathology, Massachusetts General Hospital Boston
Amino Acid Laboratory, Massachusetts General Hospital Boston
Department of Neurology, Wakayama Medical College, Wakayama, Japan
Trust Territory Health Office
University of California, Los Angeles
School of Public Health, University of Hawaii, Honolulu
Unit on Neurology, NIMH

Man Years:

Total:	1
Professional:	3/4
Other:	1/4

Project Description:

Objectives: To determine the cause of ALS and PD and to determine the epidemiological, clinical, neuropathological, and physiological significance of these diseases.

Methods employed: Routine methods for epidemiological, clinical, and neuropathological investigations.

Major findings: There is no indication that ALS or PD are declining on Guam. Our case load of neurologic patients as of December 31, 1968 was 44 ALS patients, 22 PD patients and 31 ALS or PD suspects. In addition, we are following patients with Myotonia Dystrophica, Charcot-Marie-Tooth disease, epilepsy and other rare syndromes which we have encountered. Of eight ALS deaths we secured posts on seven and of 13 PD deaths we secured posts on 11. We also collected CNS material from 16 patients who died from non-neurological causes to serve as control material. Since we have no neuropathologist on our staff and the Institute has not been able to make neuropathological services available to us, very few of the patients on whom autopsies were performed have been examined. The problem imposed by this lack of neuropathologic work-up has been discussed in many conferences and memos and I will not dwell on the subject here. At present, our key cases are still reviewed by Dr. Asao Hirano, Montefiore Hospital, Bronx, and a few of our "control" brains are being reviewed by Dr. E. Pearson Richardson, Assistant Professor of Neuropathology, Massachusetts General Hospital, Boston.

Significant new information has come to light concerning our investigations of ALS and PD on Guam since the last report. Perhaps the most exciting finding was made in studies of cerebral spinal fluid amine levels which we are conducting in collaboration with Dr. Thomas Chase, Chief, Unit on Neurology, National Institute of Mental Health. Preliminary evidence suggests that PD patients of Guam have virtually no dopamine metabolism and level of serotonin metabolism is low. Should these studies prove correct, it would indicate that several major metabolic pathways are deficient among PD patients of Guam. ALS patients and normal controls also show some abnormalities, but to a lesser extent than the PD patients.

A second significant finding is related to my trip to the Philippines. We have one Filipino (Manuel Naidas) who lived on Guam for 20 years and died with classical ALS. Dr. Asao Hirano conducted a detailed neuropathologic study of this patient and in addition to finding the expected changes of ALS he found a scattering of

neurofibrillary changes in the areas where he routinely encounters these changes among Chamorro patients. We are arranging to receive autopsy material from ALS patients on the Philippines and are reviewing Filipino patients who died of ALS in the United States. To date, we know of three Filipino ALS patients in whom neurofibrillary changes were not found. The Japanese continue reporting neurofibrillary changes in their ALS patients. If the Filipino ALS patients routinely have neurofibrillary changes this would mean that ALS in Guam, the Philippines, and Japan differs in some way from that encountered in the rest of the world. If, on the other hand, the Filipino patients do not have neurofibrillary changes it would imply that the Filipino ALS patient who died on Guam acquired his disease (or at least the neurofibrillary changes) as a result of residence on Guam.

Several genetic studies continue. We completed a preliminary analysis on the offspring of the first 100 deaths from ALS and the first 100 deaths from PD matched with the offspring of a similar number of people who died during the same yearand were born within five years of the index patient. Large and puzzling differences exist in the frequency of ALS and PD and also in the frequency of deaths from other causes among these offspring. The familial trends of ALS and PD are shown, but most of the offspring have not reached the age of susceptibility to these diseases. As a result, we are now preparing a very careful registry of all living individuals and of the exact dates of birth and death and causes of death of all the offspring of the cases and controls. A second genetic study being performed by Dr. Roswell Eldridge, Head, Section on Genetics in Epidemiology, Epidemiology Branch, C&FR, NINDS, involves the careful following of offspring of families in which both parents died of ALS or of PD on Guam. Again, this study will require several more years follow-up, since relatively few of the offspring have reached the age of susceptibility.

Studies in the Trust Territories for ALS and PD have revealed no new information. The five Carolinian patients on Saipan with possible primary lateral sclerosis are still alive and relatively unchanged clinically (see above). The census of the Trust Territory performed by the Peace Corps under the direction of the University of Hawaii in 1967 included a question for all deaths having occurred in the previous year. Through an arrangement with Dr. William Peck, Director of Public Health, Trust Territory of the Pacific Islands, Dr. Emmanual Voulgaropoulis, Head, International Program, School of Public Health, University of Hawaii, Honolulu, has turned over a complete list of deaths of individuals over age 40. We fear there is significant underreporting, but we are arranging to have follow-up information on these individuals secured in order to determine if any died of ALS or PD. Even with considerable underreporting, these data may be valuable when one considers that on Guam, if we conducted a similar study for all deaths over age 40, approximately 25% would be from either ALS or PD.

Several studies of neurologic diseases on Guam other than ALS or PD have been completed or are nearing completion. A most significant finding is that although we have about 200 patients who died

of PD we have never had a Chamorro with the classical Parkinson's disease. During the years of our study we should have had no fewer than thirty such patients. The implication from this is that the basic metabolic abnormality on Guam is so much more severe than the relatively milder abnormality which results in paralysis agitans that the latter is totally masked. If this hypothesis is correct, I believe it would be the first instance in which the clear suppression of one disease by another will be documented.

Significance to biomedical research and the program of the Institute: In Guam we have perhaps the highest incidence in the world of motor neuron disease and of a primary CNS degeneration. The documentation of the epidemiological, clinical, and neuropathological aspects of ALS and PD, a major neuromuscular disease and an important primary CNS degeneration have added to the world's knowledge concerning these neurologic diseases. In fields in which there are no known causes and no known cures, data such as these provide one of the most likely avenues for development of concepts and facts which lead to causes and cures.

Proposed course: Our most important recent finding has been observation of major metabolic defects in dopamine and serotonin metabolism among PD patients. Follow-up of this could well establish the nature of the disease or diseases which we are seeing on Guam. The neuropathologic finding of a Filipino with ALS with neurofibrillary changes is a second key observation which requires intensive neuropathologic follow-up. We have made arrangements to secure pathologic specimens from the Philippines. Lacking our own neuropathologic competence limits this study and the more vital study of brains of "control" Guamanians who have neither ALS or PD, but show neurofibrillary changes. Our study of inborn areas of metabolism has been relatively unfruitful to date. Only half the study is complete and hopefully we will find unusual patterns of inborn errors of metabolism in Guam or the Trust Territories. The epilepsy studies on Guam will be useful both as a methodologic model and as a description of this disease in a well studied population. Our access to patients and the relative ease of follow-up make Guam a particularly good area for more definitive epilepsy studies. Our genetic studies will take several years to complete, but the suggestion now that a detectable metabolic error may be involved causally in the Guam diseases increases the importance of this approach since in many metabolic diseases, there is a strong genetic component.

Finally, I would like to recommend that an increase in financial assistance and staff be provided for Guam to take advantage of the unique opportunities for stroke studies in the Trust Territories. With relatively little cost to the Institute most important and definitive findings concerning stroke patterns and high risk factors could be identified in the next few years.

Honors and Awards: None

Publications: Brody, J.A. and Chen, K.: Changing epidemiologic patterns of amyotrophic lateral sclerosis and parkinsonism-dementia on Guam. Motor Neuron Diseases, Grune & Stratton, 1969, pp. 61-79.

Serial No. NDS (CF) - 63 E 1103
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neurological diseases other than ALS/PD on Guam

Previous Serial Number: Same

Principal Investigator: Kwang-ming Chen, M.D.
NINDS Research Center

Other Investigators: Jacob A. Brody, M.D.
Leonard T. Kurland, M.D.
Mayo Clinic

Cooperating Units: NINDS Research Center, Agana, Guam
Mayo Clinic, Rochester, Minnesota

Man Years:

Total:	1/4
Professional:	3/16
Other:	1/16

Project Description:

Objectives: A survey in 1954 by Donald W. Mulder, M.D. and Leonard T. Kurland, M.D. gave the impression that not only ALS but also other heredo-familial neurologic disorders seemed unusually prevalent while multiple sclerosis and perhaps CNS tumors are uncommon. The objective of this study is to try to determine the validity of this data.

Methods employed: Since the establishment of this Center in 1956, we have occupied a unique position on Guam. It is the only neurological consultation service available to all ethnic groups on Guam and sees most neurological patients at Guam Memorial Hospital and Naval Hospital. Therefore, it is expected that most of the significant neurological cases are eventually brought to our attention. By this unique position we hope to determine the frequency of various heredo-familial neurological disorders on the island.

Major findings: From 1960 through 1966, in conjunction with ongoing studies of amyotrophic lateral sclerosis and parkinsonism-dementia on Guam, 1,028 Chamorro patients were referred to our neurologic clinic which served the entire island for diagnosis and treatment of all neurologic diseases. In comparison with other populations and particularly that of Rochester, Minnesota, the residents of Guam had higher rates of convulsive disorders,

myotonic dystrophy, peroneal muscular atrophy, and hereditary ataxias. There was no indication of an unusual incidence of central nervous system neoplasms, and no cases of progressive muscular dystrophy, myasthenia gravis, or indigenous multiple sclerosis were seen. No patient with proved classic paralysis agitans was observed in the Chamorro population.

Significance to biomedical research and the program of the Institute: This study adds to the general body of knowledge being collected by the Branch regarding the island of Guam and provides information on diseases possibly related to ALS and PD.

Proposed course: We are expanding studies of neurologic diseases on Guam and the Trust Territories using the same techniques.

Honors and Awards: None

Publications: Chen, K.W., Brody, J.A., Kurland, L.T., Patterns of Neurologic Diseases on Guam, Arch. Neurol. 19:573-578, 1968.

Serial No. NDS (CF) - 66 E 1254
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Comparison of ocular characteristics among monozygous and dizygous twins

Previous Serial Number: Same

Principal Investigator: J. Theodore Schwartz, M.D.

Other Investigator: Frank H. Reuling, Jr., M.D.

Cooperating Units: None

Man Years:

Total:	1 1/4
Professional:	3/4
Other:	1/2

Project Description:

Objectives: To develop a local register of twins as a resource for ophthalmic investigations on the heritability of ocular characteristics, and to undertake case-control studies and studies of the early natural history of chronic disorders.

Methods employed: This Section has compiled a registry of over 600 pairs of monozygous and dizygous twins who will be available for ophthalmic examination. The twin population is being interviewed and given a general eye examination. Blood type, fingerprints and ocular photographs are being obtained. On the basis of information developed through the first examination, subsets of the twin population are to be invited to participate in specific investigations.

Major findings: Ocular abnormalities found among the twin population are being compiled. A series of twins with normal visual acuity and negative history for eye disease has now been compiled for selection of twins to participate in the study of the inheritance of the hypertensive reaction to topically instilled corticosteroid (steroid) eye drops. A subset of young identical twins concordant for myopia is being assessed to study the influence of treatment on the progress of myopia. The

following investigations are being undertaken in collaboration with other institutes: 1) a study of genetic factors in cardiovascular diseases being undertaken by the Field Epidemiologic Research Section of the N.H.I., 2) a study of fetal loss associated with Xg^a blood type incompatibility between mother and offspring, undertaken in collaboration with the Children's Diagnostic and Study Branch of NICHD, and 3) a study of the heritability of blood lipid characteristics being undertaken by the Molecular Disease Branch, N.H.I.

Significance to biomedical research and the program of the Institute: Comparison of concordance of physical characteristics among MZ and DZ twins is valuable as an indication of the relative roles of heredity environment in the expression of these characteristics.

Proposed course: Additional investigations will be carried out on selected pairs of twins. Early studies will investigate parameters of ocular motility, including a study of heterophoria, ACA ratio, vergence amplitudes and accommodation amplitudes. Expansion of the twin register through collaboration with the USPHS Hospital, Baltimore will be undertaken to identify additional twinships having specific ocular affections.

Honors and Awards: None

Publications: Twin Studies in Ophthalmology; Hereditary and Environmental Determinants of Eye Disease. American Journal of Ophthalmology, Vol. 66, No. 2, 1968.

Serial No. NDS (CF) - 64 E 1257
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: A study of mortality in the U.S. from malignant neoplasms of the eye

Previous Serial Number: Same

Principal Investigator: J. Theodore Schwartz, M.D.

Other Investigators: David L. VerLee, M.D.
Irving D. Goldberg, Ph.D.
National Institute of Mental Health

Cooperating Units: Office of Program Planning and Evaluation, NIMH
Biometrics Branch, C&FR, NINDS

Man Years:

Total:	0
Professional:	0
Other:	0

Project Description:

Objectives: To study the U.S. mortality experience with malignant tumors of the eye.

Methods employed: Under the present system of classifying causes of death, all fatalities due to malignant neoplasms of the eye or optic nerve are assigned without subclassification to Rubric 192. Retrospective characterization of eye tumor mortality by histologic type requires, therefore, an examination of individual death certificates.

In the U.S. during the period 1959 to 1961, there were 1,108 certificates in which the primary cause of death was assigned to Rubric 192. A full copy of the microfilm image of these death records has been provided by the Division of Vital Statistics, National Center for Health Statistics, on 1,024 certificates. The data from these records has been recorded in a standard format and is now being analyzed. Additional information necessary to classify the diagnosis listed on the death

certificate has been solicited from hospitals and records and the certifying physician in certain cases.

Major findings: Compilation of the data have now been completed and final statistical tables are now available. Estimated annual mortality rate in the U.S. for malignant melanoma is 1.173 per million, for retinoblastoma 0.247 per million and for glioma of the optic nerve 0.047 per million.

Significance to biomedical research and the program of the Institute: Certain epidemiologic features of eye tumor mortality in the U.S. such as age, race, sex, and state of residence are being obtained from this analysis and prepared for publication.

Proposed course: This project is continuing. It will be reactivated when Dr. Schwartz returns to the Institute.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 66 E 1313
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Ophthalmic survey of population groups of South Pacific Islands

Previous Serial Number: Same

Principal Investigator: David L. VerLee, M.D.

Other Investigators: J. Theodore Schwartz, M.D.
Robert E. Markush, M.D.
Albert Damon, M.D.
Harvard University

Cooperating Unit: Department of Anthropology, Harvard University

Man Years:

Total:	0
Professional:	0
Other:	0

Project Description:

Objectives: To describe the ocular status of populations residing on two South Pacific Islands.

Methods employed: This Section was invited to join a survey team of medical specialists and anthropologists in the South Pacific to examine the Nasioi on the island of Bouganville in the Territory of Papua and New Guinea, and the Kwaio on the island of Malaita in the British Solomon Islands. Members of the Department of Anthropology, Harvard, had recently completed approximately two years of anthropologic study of these populations, and that Department followed this with medical and epidemiologic investigations. These investigations included general medical evaluation, evaluations in internal medicine, cardiology, pediatrics, dentistry, ophthalmology, general metabolic status, and anthropometry.

Major findings: Among the observations made were the following which are of particular interest because they differ from available data on Western populations:

1. Approximately 95% of all persons had visual acuity of 20/20 or better in the better of the two eyes.
2. Refractive errors, in particular myopia and astigmatism, were rare. Only 10 of the 1155 (0.8%) eyes were myopic, and the myopia in all 10 was 0.5 diopter or less. Astigmatism of 0.75 diopters or more was found in only 61 (5.3%) of the eyes.
3. Schiotz tonometry determinations revealed only three of 812 eyes to have intraocular pressure over 21 mm hg., the pressure in all three was 22.4 mm hg.
4. Arteriosclerotic and hypertensive retinopathy were virtually absent in all age groups.

Significance to biomedical research and the program of the Institute: While no unusual prevalence of any disease process was encountered in these populations, the apparent dissimilarities from Western populations pose interesting opportunities for further epidemiologic investigation. The presence of active trachoma among all examinees from islands neighboring an essentially trachoma-free island may warrant further investigation.

Proposed course: Discontinued.

Honors and Awards: None

Publications: VerLee, D.L.: Ophthalmic Survey in the Solomon Islands. American Journal of Ophthalmology, Vol. 66, No. 2, 1968.

Serial No. NDS (CF) - 66 E 1314
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Influence of synthetically derived aglycone of cycasin and methycholanthrene on ocular tissues

Previous Serial Number: Same

Other Investigator: Frank H. Reuling, Jr., M.D.

Other Investigators: J. Theodore Schwartz, M.D.
Gert L. Laqueur, M.D.
Experimental Pathology Branch, NIAMD
David W. Smith, M.D.
Experimental Pathology Branch, NIAMD

Cooperating Unit: Experimental Pathology Branch, NIAMD

Man Years:

Total:	1/12
Professional:	1/12
Other:	0

Project Description:

Objectives: To study the influence of synthetically derived aglycone of cycasin and methycholanthrene on ocular tissues.

Methods employed: Investigators at NIAMD have shown that the aglycone of cycasin (hydroxyazoxymethane) and other derivatives of the cycad nut can produce hepatic, renal, gastric, pulmonary and cerebral tumors in certain experimental animals. Methylcholanthrene is known to be capable of producing intraocular tumors in the rat.

Techniques of intracameral injection and implantation have been developed and a rabbit population has been exposed to the above agents.

Major findings: Aglycone of cycasin: 33 infected rabbits developed a vasculitis of the retinal vessels which when graded as to severity appears to correlate with dosage. No tumors have been noted to date.

Methylcholanthrene: 12 rabbits given intravitreal injection of methylcholanthrene and observed for a period of nine months failed to demonstrate a clinical response to this drug.

Significance to biomedical research and the program of the Institute: To date this experiment has been negative for tumor formation. A positive outcome would provide evidence for oncogenic capability of hydroxyazoxymethane in "sterile" tissues. It would also provide a laboratory model for experimentation in intraocular tissues.

Proposed course: Twelve rabbits selected on the basis of total injected dosage and total observation time are being followed for tumor formation. Twenty-one rabbits have been sacrificed and pertinent tissues have been retained for pathologic studies.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 66 E 1319
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: A search for autoimmune mechanisms in the pathogenesis of chronic neurological diseases by the use of peripheral lymphocytes

Previous Title: Determining autoimmunity in chronic neurological diseases by the use of peripheral lymphocytes

Previous Serial Number: Same

Principal Investigators: Jacob A. Brody, M.D.
George Nemo, Virologist

Other Investigators: Martha Christofili, Biologist
Minnie Toure, Biologist

Cooperating Units: None

Man Years:

Total:	1/4
Professional:	1/12
Other:	3/12

Project Description:

Objectives: To develop a simplified quantitative method to measure lymphocyte transformation reactions in vitro, and to apply the technique to the study of various neurological diseases with the hope of implicating an autoimmune mechanism in the pathogenesis of these disorders.

Methods employed: Presently, the lymphocyte transformation phenomenon is measured autoradiographically in our laboratory. Although the technique is generally accepted it is quite laborious and time consuming. Consequently, studies have been undertaken to devise a simpler, less time consuming method based upon spectrophotometry. Biochemical color reactions designed to measure total desoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein content of lymphocyte cultures are being employed.

Major findings: Preliminary data indicate that the diphenylamine color reaction designed to measure total DNA content may be employed as a measure of lymphocyte transformation in vitro. Cultures stimulated with the appropriate antigens show a quantitative increase in total DNA content.

Significance to biomedical research and the program of the Institute: The development of a rapid, simplified screening technique to measure the degree of lymphocyte transformation will permit more efficient and less time consuming surveys of lymphocyte transformation reactions from chronic neurological disease cases.

Proposed course: A study is presently underway to determine the effect of various antigens found in brains of normal individuals and patients with MS upon peripheral lymphocytes. Also, a number of studies designed to determine factors which cause a depression of the lymphocyte response are under way. Lymphocytes from individuals on steroid therapy or following attenuated measles vaccination will be tested for an impaired lymphocyte response using phytohemagglutinin as a stimulant. A similar approach will be employed using lymphocytes from MS patients in acute exacerbation.

Honors and Awards: None

Publications:

Brody, J.A., Harlem, M.M., Plank, C.R., and White, L.R.: Freezing human peripheral lymphocytes and a technique for culture in monolayers. Proc. Exp. Biol. & Med. 129:968-972, 1968.

Brody, J.A., Harlem, M.M., Kurtzke, J.F., and White, L.R.: Unsuccessful attempt to induce transformation by cerebrospinal fluid in cultured lymphocytes from multiple sclerosis patients. New Eng. J. Med. 279:202-204, 1968.

Serial No. NDS (CF) - 66 E 1320
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Stateside Guamanian study

Previous Serial Number: Same

Principal Investigators: Roswell Eldridge, M. D.
Jacob A. Brody, M. D.

Other Investigator: Elizabeth Ryan, R. N.

Cooperating Units: NINDS Research Center, Agana, Guam
School of Public Health, University of California, Berkeley

Man Years:

Total:	1/2
Professional:	1/6
Others:	5/12

Project Description:

Objectives: This study was instituted in July 1966 to determine if ALS and PD occur with the same high frequency among Guamanians who have left Guam. Since the bulk of the stateside Guamanians are in California, efforts have been concentrated there.

Methods employed: A household census was completed in the fall of 1967 which included information on neurologic disease. Names of heads of households were obtained from relatives on Guam, the office of the Guamanian representative to Congress, local Guamanians, social organizations, an eight year old NINDS California Guamanian registry and from other Guamanians already living in this country. Household information was obtained by trained Guamanian interviewers living in California and by personnel from the Branch. Follow-up examination of suspect cases of ALS and PD was conducted by specialist physicians.

Major findings: A total of 370 households have been interviewed with demographic and medical information obtained on their 1,853 occupants. Two cases of ALS and two probable cases of PD were found indicating the frequency of these two diseases is similar in this migrant population to that on Guam. Diabetes, gout, renal stone, hypertension and peptic ulcer disease were encountered frequently.

Significance to biomedical research and the program of the Institute: The results suggest that a genetic factor and/or early exposure to an environmental factor is responsible for ALS and PD on Guam. Thus, efforts on Guam should be directed specifically at these two areas.

Proposed course: Evaluation of metabolic and mental disease in this migrant population is being pursued by the School of Public Health, University of California, Berkeley.

Honors and Awards: None

Publications:

Eldridge, R., Rosario, J. and Brody, J. A.: Amyotrophic Lateral Sclerosis and Parkinsonism Dementia in a Migrant Population from Guam. (A preliminary report). In Transactions of the American Neurological Association. New York, N. Y., Springer Pub. Co., 1968, Vol. 93, pp. 204-206.

Eldridge, R., Ryan, E., Rosario, J. and Brody, J. A.: Amyotrophic Lateral Sclerosis and Parkinsonism Dementia in a Migrant Population from Guam. (A full report) Neurology (In press).

Serial No. NDS (CF) - 66 E 1321
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Japanese B encephalitis studies on Guam

Previous Serial Number: Same

Principal Investigators: George Nemo, Virologist
Jacob A. Brody, M.D.
C. Joseph Gibbs, Ph.D.
Laboratory of Slow, Latent, and Temporate Viruses

Other Investigator: None

Cooperating Unit: Laboratory of Slow, Latent, and Temperate Viruses, C&FR, NINDS - NDS (CF) - 63 OAD 1140

Man Years:

Total:	3/4
Professional:	1/4
Other:	1/2

Project Description:

Objectives: A Japanese B encephalitis epidemic occurred on Guam in 1947 and 1948. Subsequently there was evidence that the virus completely disappeared from Guam which is almost unprecedented in ARBO virus ecology. Recently a very efficient mosquito vector of JBE the Culex tritaeneorhincus has appeared in large numbers on Guam.

Our studies are divided into three major areas. (1) The long-term neurological and psychological effects of JBE on individuals who suffered from clinical illness and particularly among individuals who suffered from subclinical or inapparent infections. (2) Serological studies of JBE antibodies to determine their persistence and to evaluate the most sensitive methods for detection. (3) To determine if the virus completely disappeared on Guam and, if not, to study the ecology of this agent in an apparently hostile environment.

Methods employed: A large number of sera from humans and animals have been screened against JBE antigen by the hemagglutination inhibition technique. Those positive sera and selected negative ones are also being checked by complement fixation and tissue culture neutralization techniques.

Major findings: Of 492 sera examined, 113 (22.97%) had HI antibody to JBE virus. Of those born before 1950, 106 out of 371 (28.57%) are positive, whereas only 5.79% (7 out of 121) of those born after 1950 have a discernible antibody titer. Complement fixation studies and tissue culture neutralization studies are now underway to determine the specificity or sensitivity of the HI responses.

Significance to biomedical research and the program of the Institute: This project will produce new information on JBE as outlined under "Objectives" by exploiting the unique situation of a single epidemic and subsequent disappearance of JBE on Guam.

Proposed course: It is proposed that when the present laboratory investigations are completed, these specimens be examined with antigens of other viruses of the ARBO B group. Also, when clinical examinations of those people with significant titers are completed, some conclusions can be made about the neurological sequelae of subclinical JBE infections.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 66 E 1322
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Otitis media and hearing loss on Guam

Previous Serial Number: Same

Principal Investigators: Roswell Eldridge, M. D.
Jacob A. Brody, M. D.

Other Investigator: Eldon L. Eagles, M. D.
Assistant Director, NINDS

Cooperating Unit: Office of the Assistant Director, NINDS

Man Years

Total:	2/3
Professional:	1/6
Other:	1/2

Project Description:

Objectives: A three phase study was begun in 1966 to determine the contribution made by otitis media to the high rate of hearing loss on Guam.

Methods employed: 1. 1,541 school children were tested in May 1966 and seven months later those with hearing loss were retested and examined. They were also questioned about ear, nose and throat symptoms and given a physical examination with emphasis on otologic findings.

2. The selective service records of 350 Guamanian men examined in 1966 were reviewed for ear disorders.

3. A one year prospective study beginning in February 1966 on a sample of children born since 1961 was conducted to determine the morbidity from otitis media.

Major findings: 1. Sixteen and eight-tenths percent of those screened had a hearing loss compared to three to five percent of those in U. S. and Canadian studies. More than half of those examined had evidence of otitis media and perforation of the drum was common.

2. More than a third of those examined by selective service on Guam had at least mild hearing loss and one in six

of those medically disqualified had severe loss and/or perforation of the drum, a much higher frequency than in those medically disqualified in the U. S.

3. In contrast to findings in the first two phases, questioning about symptoms of ear infections indicates there is little morbidity related to ear infection in preschool age children.

Significance to biomedical research and the program of the Institute: The unusual pattern of morbidity in this tropical setting suggests that the causative organism and/or the host response may be unique. A major public health campaign would probably be the most effective method to reduce the high rate of otitis media on Guam.

Proposed course: These results have been made known to the Public Health Service of the Government of Guam. This group should best be able to bring this problem to the attention of appropriate medical personnel on the island and to initiate a program of education of parents about the signs of this potentially crippling process. They may also be able to undertake the microbiologic search for the responsible agent.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 67 E 1325
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: One year experience of all births on Guam with special reference to diabetic complications

Previous Serial Number: Same

Principal Investigators: Jacob A. Brody, M.D.
R. Michael Scott, M.D.
Joyce M. Cannon, R.N.

Other Investigators: Jerome Deutschberger
Office of Biometry
Anne Kantor
Office of Biometry

Cooperating Units: NINDS Research Center, Agana, Guam
Office of Biometry, OD, NINDS

Man Years

Total:	1/4
Professional:	1/12
Other:	1/6

Project Description:

Objectives: The present project was designed to expand the scope of this study by analyzing all births for one year. During the year 1965 there were 2,523 births and we compiled data on date of birth, place of birth, birth weight, birth order, length of gestation, birth defects, age and race of parents, maternal complications such as diabetes, etc.

Methods employed: A study by Yen in 1963-64 revealed an unusually high incidence of abnormal carbohydrate metabolism during pregnancy among the native population of Guam. He also found that obesity and large babies appeared to be a constant finding in mothers with abnormal carbohydrate metabolism and were connected with an increased incidence of maternal and perinatal complications.

Major findings: These data are currently being analyzed in order to determine whether the high incidence of diabetes has an appreciable effect on the birth weight.

Significance to biomedical research and the program of the Institute: The data will be of value for public health and anthropological studiea.

Proposed course: The data on this project are presently being analyzed by Mrs. Kantor's office. We anticipate full tabulations of this material in the very near future.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 67 E 1485
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Analyses of abnormal urine and blood amino acids metabolism among Guamanians

Previous Serial Number: Same

Principal Investigators: Edward W. Brink, M.D.
NINDS Research Center
Vivian Shih, M.D.
Massachusetts General Hospital

Other Investigators: Jose M. Torres
NINDS Research Center
Manuel T. Cruz
NINDS Research Center

Cooperating Units: NINDS Research Center, Agana, Guam
Amino Acid Laboratory, Massachusetts General Hospital
Boston, Massachusetts

Man Years

Total:	1/6
Professional:	1/12
Other:	1/12

Project Description:

Objectives: Earlier observation indicated that indigenous Guamanians have difficulties in handling protein and carbohydrate. However, the relationship between the observed hyperuricemia and hyperglycemia on Guam and the neurologic manifestations is not clear.

Methods employed: A contract with the Amino Acid Laboratory of the Massachusetts General Hospital for the broad testing for inborn errors of metabolism was secured and blood and urine are being sent to the lab from Guam.

Major findings: To date, 590 blood and urine specimens have been sent to Dr. Shih's lab. We were disappointed that no unusual amino acid patterns have been encountered in our Guam patient population or the infant population. We do have a few suspects on several of the Trust Territory Islands. It is possible that children with severe abnormalities died before we were able to conduct the screening. However, since the populations we are working with are

relatively isolated, I would have expected a fair yield from this approach. Perhaps before the end of the study we will encounter interesting abnormalities in these isolated populations.

Significance to biomedical research and the program of the Institute: This study is contributing to the general knowledge of the Chamorro people of Guam.

Proposed course: This project is continuing.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 67 E 1486
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Torsion Dystonia - a clinical and genetic study

Previous Serial Number: Same

Principal Investigator: Roswell Eldridge, M. D.

Other Investigators: Irving S. Cooper, M. D.
St. Barnabas Hospital
Morris B. Gross, M. D.
Hunter College in the Bronx
Wolfgang Zeman, M. D.
University of Indiana
Mary Bazelon, M. D.
Childrens Hospital
Anne Harlan

Cooperating Units: Department of Neurologic Surgery, St. Barnabas Hospital, New York
Department of Education, Hunter College in the Bronx, New York
Department of Neuropathology, University of Indiana Medical Center, Indianapolis
Childrens Hospital, Washington, D. C.
Section on Genetics in Epidemiology, Epidemiology Branch, NINDS

Man Years

Total:	1
Professional:	2/3
Other:	1/3

Project Description:

Objectives: Torsion dystonia (TD) comprises a heterogeous group of conditions characterized by disorder of movement due to either genetic or environmental factors. Earlier studies suggest one form is inherited as an autosomal dominant and that, surprisingly, it is four times more common in those with Jewish ancestry. The present study was undertaken to define further the nosology of these conditions in order to determine the basic defect in each.

Methods employed: Probands with a history of TD were selected through 180 neurologic and neurosurgical centers and provided the families for study. A detailed family history was obtained stressing geographical origin of ancestral couples and the proband and all available relatives were given physical examinations. Patients from all areas of the U. S. and treated by various methods were seen to avoid geographic, ethnic, and therapeutic bias.

Major findings: Over 500 individuals in 100 families have been examined. One hundred and fifty have dystonia on clinical grounds and an additional 60 who are dead or unavailable are considered affected on the basis of photographs and/or history.

Formal genetic analysis indicates two distinct hereditary patterns: the previously recognized autosomal dominant; and autosomal recessive which has not been recognized heretofore.

An autosomal recessive form of TD is indicated by at least six observations including the unusual proportion of Jewish families in which TD occurs in only a single generation and clinical differences between patients in this group and the autosomal dominant group with symptoms in the former tending to appear earlier and to be more severe.

Striking among the clinical aspects of TD was the high frequency of misdiagnosis of psychiatric illness during the early stages of the disease. At least 30 of the 100 probands had prolonged periods of unrewarding psychotherapy. Notable also was the role of various forms of stress in precipitating or aggravating the symptoms of TD. Finally, simple intention tremor in ancestors of those with TD was seen in four Jewish and four non-Jewish families.

The mutation rate for the dominant form is relatively low (approximately one per million gametes). The recessive form of the disease occurs in the Jewish population with a frequency of about one per 40,000 births so that one in 100 in this population is a carrier.

It is imperative that physicians are aware that TD may exist in at least two different hereditary forms since prognosis and risks to subsequent offspring are different in each.

Significance to biomedical research and the program of the Institute: Elucidation of the fundamental defect in these forms of dystonia will be of practical importance since it should be possible to distinguish between the recessive and dominant forms chemically. The application to genetic counselling of such a test is obvious. As in other inborn errors of metabolism, such a study could provide basic, new information about central nervous system physiology. Parkinson's disease shares certain clinical features with dystonia and is relieved by the same operative procedure so that information gained from the dystonia study may bear on this important problem.

Proposed course: Physiologic and biochemical parameters are being investigated in select families. Studies are in progress on six patients from this series. A defect in the catecholamine-serotonin series is indicated. Preliminary tests on another patient with a variant of TD suggest a new disorder of intermediary metabolism due to abnormal methylation which is responding to penicillamine therapy.

The IQ is unusually high in patients with the recessive form of TD. To date the study group consists of 24 individuals. Individual IQ scores in the patient group range from 111 to 170 with a mean of 131 and a standard deviation of 17.3. The controls for this group have scores ranging from 92 to 127 with a mean of 113 and standard deviation of 13.8. The difference between the mean IQs for these two groups is significant at a level of P=.04. Siblings have scores ranging from 97 to 146 with a mean IQ of 118 and standard deviation of 11.4. Their control group has an IQ range of 91 to 127 with mean of 108 and standard deviation of 15.7. The difference between these two groups is not statistically significant with P=.09.

Analysis of achievement tests indicate that, in general, both reading and mathematical performance are higher in patients and sibs than in their respective control groups. No difference was found between the mathematical achievement and the reading achievement of patients or sibs.

Contrary to the reported association of TD with mental retardation, this study of intelligence in a small group of cases of autosomal recessive TD indicates those with this disorder perform better intellectually than an unaffected but otherwise similar population. If there is an intellectual advantage conferred by the gene, this would explain the gene's high frequency in a population which over many generations may have been unusually sensitive to selection based on intelligence.

This may have dramatic implications and will further add impetus to the search for the chemical expression of the gene.

There are several foci of dystonia in other parts of the world, notably northern Sweden, Israel and southern Italy. Their clinical and genetic study might be equally revealing.

A special report is planned emphasizing the frequent misdiagnosis of early TD as a psychiatric disorder and the harm this does to patients and their families.

Honors and Awards: One of six finalists for outstanding clinical research sponsored by the Clinical Society and COA, USPHS.

Publications:

Eldridge, R., Ryan, E., Brody, J. A. and Cooper, I. S.: Dystonia Musculorum Deformans: Evidence for two hereditary forms. Proc. II Internatl. Congr. of Neuro-Gen. and Neuro-Ophthal. - Montreal. 1967. pp 772-788. (In press)

Eldridge, R., Harlan, A., Cooper, I. S. and Riklan, M.: The Hereditary Torsion Dystonias (Dystonia Musculorum Deformans): Geographical distribution and I.Q. in dominant and recessive forms. In Transactions of the American Neurological Association, 94. (In press)

Serial No. NDS (CF) - 67 E 1487
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Genetic analysis of family data on Guam ALS cases

Previous Serial Number: Same

Principal Investigators: Roswell Eldridge, M. D.
James A. Schnur, M. D.

Other Investigator: Manuel T. Cruz
NINDS Research Center

Cooperating Unit: NINDS Research Center, Agana, Guam

Man Years

Total:	1/4
Professional:	1/6
Other:	1/12

Project Description:

Objectives: To utilize the accumulation of 20 years of experience for an indepth genetic analysis of pedigree information of Guam ALS.

Methods employed: Pedigrees were developed for the 370 definite cases of Guam ALS by Guamanian practitioners aware of actual biologic parents. Of these 70 were suitable for segregation analysis. Also examination was made of sibs whose parents were both affected by ALS.

Major findings: The initial data indicate that Guam ALS may be inherited as a simple autosomal recessive trait. In 46 families suitable for test of the autosomal recessive hypothesis, 64 cases were observed while 74 cases would be expected from truncate analysis. The 95% confidence limits for such analysis cover the range from 64 cases to 84 cases so the observed number of cases is compatible at this level of significance although barely so.

Two of 13 over 35 years of age whose parents both had ALS were found to have signs compatible with early ALS. If ALS is recessive all such offspring should eventually be affected.

In testing for the autosomal dominant hypothesis in the 16 families suitable for this analysis, nine cases were observed, 27

would be expected and 19 to 35 cases would be the range at a 95% limit confidence. Therefore, autosomal dominant inheritance is possible only if one postulates the gene is not penetrant (i.e., there is no expressing of the disease) in 50% to 70% of those carrying it.

Troublesome to any simple mode of inheritance postulated is the 2:1 male to female ratio of ALS patients. A finding which may answer this discrepancy and possibly shed light on the basic process of the disease is that in these siblings there is an excess of female deaths under one year of age.

Significance to biomedical research and the program of the Institute: Obviously establishing a genetic basis for Guam ALS would have far-reaching consequences. The elusive question of the cause of Guam ALS would be answered. A new genetic disease would be added to the expanding catalogue of inherited neurologic diseases. Efforts of the Branch on Guam could be concentrated on other problems such as the PD question and its relation to the pattern of metabolic disease on the island. A search could be made for other isolated populations where the gene might also be frequent.

Proposed course: Complete information is being obtained on pedigrees of other Guam ALS cases so as to increase the sample studied. Detailed study of offspring now at risk of specific mating types is underway.

Since a number of Filipinos of Guam have ALS and in the past the Filipinos were a major source of repopulation of the island, a search for an ALS focus on Luzon will be made.

A similar genetic analysis of PD will be undertaken.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 67 E 1488
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Serological studies of common viruses and genotyping in cases of multiple sclerosis (MS) and controls

Previous Serial Number: Same

Principal Investigators: Jacob A. Brody, M.D.
John L. Sever, M.D.
Perinatal Research Branch, NINDS
Joyce Cannon, R.N.

Other Investigators: Mark Dyken, M.D.
Neurology Department, Indiana University Medical Center
A. Donald Merritt, M.D.
Department of Medical Genetics, Indiana University Medical Center
Jerome Deutchberger
Office of Biometry, NINDS
Anne Kantor
Office of Biometry, NINDS

Cooperating Units: Section of Infectious Diseases, PRB, NINDS
Neurology Department, Indiana University Medical Center, Indianapolis
Department of Medical Genetics, Indiana University Medical Center, Indianapolis
Office of Biometry, OD, NINDS

Man Years:

Total:	2-1/6
Professional:	1-1/6
Other:	1

Project Description:

Objectives: To test the hypothesis that MS may be caused by an unusual response to a common virus infection. To search for possible distortions of segregation and association between MS and one or more genetic markers.

Methods employed: MS patients known to the Neurology Department, IUMC and to the Indiana Chapter of the National Multiple Sclerosis Society were contacted and asked to participate. In addition for each case several controls with similar backgrounds and infectious disease experience were selected. Suitable controls are: sibling near the age of the patient, a classmate friend of the patient who grew up in the same community, and the patient's spouse. All patients used in the study were personally examined by one of the two clinical neurologists participating in the study to verify the diagnosis. Patients and controls answered standard questions regarding infectious disease, environment, course of illness and family history and blood specimens were taken.

Serological analysis is being conducted in the Section of Infectious Diseases, PRB, NINDS using a battery of common virus antigens by hemagglutination and complement fixation methods. Differences between the patient and his controls and similarities among the patients will be sought.

Genotyping is being done by the Department of Medical Genetics, IUMC for approximately 20 polymorphic systems including blood groups, erythrocytic enzyme and serum protein evaluations.

A portion of the frozen serum is being banked to test promising hypotheses in the future.

Major findings: Perhaps an important break-through has developed. The MS patients have higher titers to both measles and mumps. These do not appear to be cross-reactions. The one group, however, with titers as high as patients are their sibs. This implies either a peculiar family response, a different virus or a combined infection within the family.

Significance to biomedical research and the program of the Institute: The serological studies whether results are positive or negative will give valuable information regarding the role of viruses in the etiology of MS. Adequate genotyping of MS patients and their families has not been reported. The proclivity to develop MS may be associated with a testable genetic marker.

Proposed course: The project will be extended to investigate more thoroughly the relationship of family to MS patient.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 67 E 1489
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neuropathological studies in veterans dying of ALS who served on Guam

Previous Serial Number: Same

Principal Investigators: Jacob A. Brody, M.D.
R. Michael Scott, M.D.

Other Investigators: Kenneth Earle, M.D.
Armed Forces Institute of Pathology
Asao Hirano, M.D.
Montefiore Hospital
Joseph Seggora, M.D.
Veterans Administration Hospital
F. A. Quadfasel, M.D.
Veterans Administration Central Office

Cooperating Units: Neuropathology Branch, Armed Forces Institute of Pathology, Washington, D.C.
Department of Neuropathology, Montefiore Hospital New York
Veterans Administration Hospital, Boston
Neurology Section, Veterans Administration Central Office, Washington, D.C.

Man Years:

Total:	1/3
Professional:	1/3
Other:	0

Project Description:

Objectives: To determine if ALS in veterans who served on Guam is an acquired disease.

Methods employed: Dr. Hirano has reported characteristic neurofibrillary changes in Guamanian ALS patients, but these changes are not seen in classical stateside ALS. Since a large number of U.S. servicemen were stationed on Guam during World War II, it is possible to examine the CNS of U.S. veterans who died of ALS who spent considerable time on Guam. The question to be answered is whether these men show the characteristic Guam-type neuropathological

changes or the classical stateside ALS changes.

Major findings: Brains from three veterans serving on Guam have been collected, and the material has been examined by Drs. Earle and Hirano who have noted the findings of "stateside" ALS only.

Significance to biomedical research and the program of the Institute: These findings are evidence that Guamanian ALS does not result from short term exposure to an environmental agent. However, the brain of a Filipino dying of ALS after being on Guam for many years has shown typical neurofibrillary changes, suggesting that length of exposure to an environmental agent may be an important factor in subsequent development of ALS (Guam).

Proposed course: This material is being prepared for publication.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 67 E 1490
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The application of fluorescent antibody methods to the study of chronic neurological disorders

Previous Title: Fluorescent microscopy using fixed, imbedded CNS tissue

Previous Serial Number: Same

Principal Investigators: Jacob A. Brody, M.D.
George Nemo, Virologist

Other Investigators: Minnie Toure, Biologist
Martha Christofili, Biologist

Cooperating Unit: None

Man Years:

Total:	1/3
Professional:	1/4
Other:	1/12

Project Description:

Objectives: To use fluorescent antibody techniques using frozen sections of CNS tissue for detection of viral antibody.

Methods employed: The two main staining techniques employed in fluorescent microscopy, the direct and indirect methods will be employed. Frozen CNS tissue sections 4-5u will be prepared using a microtome held at -16 to -18 C in a mechanically refrigerated cryostat.

Major Findings: None as yet.

Significance to biomedical research and the program of the Institute: Fluorescent antibody methods are applicable to the study of chronic neurological disorders thought to be of autoimmune etiology. The technique is useful in determining the production of autoantibodies as well as sites of delayed-type hypersensitivity reactions. A search for viral antigens and sites of viral replication in CNS tissue is also made possible using this technique.

Proposed course: To be continued.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 67 E 1494
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Influence of diurnal variation on tonometric surveys

Previous Serial Number: Same

Principal Investigator: Richard E. Goldberg, M.D.

Other Investigators: J. Theodore Schwartz, M.D.
Allen R. Lewis, M.S.
Biometrics Branch, C&FR, NINDS

Cooperating Unit: Biometrics Branch, C&FR, NINDS

Man Years:

Total:	0
Professional:	0
Other:	0

Project Description:

Objectives: To study the population trend of average intraocular pressure at different hours of the day.

In normal eyes and in eyes with glaucoma, the level of intraocular pressure does not remain constant throughout the day. Several different patterns of diurnal variations have been described. If total populations show a significant overall variation in diurnal patterns such variation could influence the outcome of tonometric surveys designed to collect comparable epidemiologic data as well as the outcome of surveys undertaken to identify glaucoma suspects.

Methods employed: In this project the measurements of intraocular pressure on 2,620 eyes as obtained in three community surveys (Nesquehoning, Penn., Colorado River Reservation, Arizona, and Salt River Reservation, Arizona) were analyzed to determine the possible existence of a significant population trend in diurnal variation. For each community, intraocular pressure measurements obtained by three different examination techniques are being analyzed separately.

Major findings: 'Analysis shows lowered pressure for those measurements taken later in the day. This trend has been consistent for each of the communities and was found to be statistically significant. This tendency is consistent with clinical knowledge of diurnal variation although the present data do not permit descrimination between an age effect and diurnal variation as an explanation of the findings.

Significance to biomedical research and the program of the Institute: The findings of the study suggest that the time of measurement can influence comparability of tonometry data collected for epidemiologic investigation.

Proposed course: This project is completed.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 67 E 1495
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Remote neurological effects of lung cancer

Previous Serial Number: Same

Principal Investigator: Elliot C. Wilner, M.D.

Other Investigator: None

Cooperating Unit: Veterans Administration, Washington, D.C.

Man Years:

Total:	0
Professional:	0
Other:	0

Project Description:

Objectives: To determine if lung cancer produces distinct syndromes of involvement of the nervous system, and if so, to determine the role and relationship between the histologic type of cancer and the various neurological syndromes.

Methods employed: The study group consisted of 106 patients from V.A. hospitals who had had the diagnosis of lung cancer made by biopsy (or by sputum cytology if biopsy confirmation was to be had later). These subjects were seen either as inpatients or as outpatients followed in clinics. The control groups consisted of 44 inpatients at the Washington, D.C. V.A. Hospital who were hospitalized for various subacute or chronic pulmonary diseases and considered not to have carcinoma. The study and control groups were roughly matched for age, duration of illness, consumption of alcohol and tobacco.

All subjects in the study and control groups were interviewed and examined neurologically. The interview served to document information about duration of illness, type of therapy, social habits, and previous illnesses, and to elicit symptoms of current neurological disease. The examination was designed to uncover signs of any of the syndromes previously ascribed to remote malignancies.

Blood specimens were obtained from six patients and may be obtained from more patients later for lymphocyte transformation studies and to be used for innoculation into laboratory animals.

Major findings: No statistically significant differences in the rate or type of unexplained neurological signs were found between cancer patients and controls; the rate among the controls was much higher than that reported of unexplained neurological signs to be independent of duration of cancer symptoms or treatment, as has been stated, but in fact with successful treatment and increased survival time the frequency declined. Finally, we did not find in this small series that oat cell carcinoma was associated with a high frequency of the myasthenic syndrome or severe peripheral neuropathy. The impression gained was that the majority of the remote neuropathies represent a nonspecific injury to the neuromuscular apparatus as a result of nutritional, endocrinological, immunological, or metabolic disturbances, and they occur in many chronic diseases including carcinoma of the lung.

Significance to biomedical research and the program of the Institute: See above.

Proposed course: This project has been completed.

Honors and Awards: None

Publications: Wilner, E.C. and Brody, J.A.: An evaluation of the remote effects of cancer on the nervous system. Neurol., 18:1120-1124, 1968.

Serial No. NDS (CF) - 67 E 1496
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Sequelae of CNS diseases in childhood

Previous Title: Sequelae of measles

Previous Serial Number: Same

Principal Investigator: Jacob A. Brody, M.D.

Other Investigator: Estelle Kornhauser, R.N.

Cooperating Units: Office of Biometry, OD, NINDS
Children's Hospital, Washington, D.C.

Man Years:

Total:	2/3
Professional:	1/3
Other:	1/3

Project Description:

Objectives: To determine if infection with viruses capable of penetrating the CNS cause permanent neurologic sequelae, particularly in those cases in which infection occurred under the age of two years.

Methods employed: As the result of previous studies we have decided to improve our methods and techniques by investigating populations in which known encephalitis occurred. Initially, we will follow up 78 patients admitted to Children's Hospital in Washington with a diagnosis of measles encephalitis. Once we have our methods worked-up we will broaden the scope of studies to other known encephalities. At present, we are attempting to contact the post-measles encephalitis children and subsequently, will conduct neurological and psychological tests upon them.

Major findings: None as yet.

Significance to biomedical research and the program of the Institute:

Although it is widely believed that infections of the CNS early in childhood produce brain damage, there are no definite patterns of brain damage or specific diseases which commonly are associated with brain damage. Documentation of specific lyrol-tropisms to learning and performance would be a major contribution to understanding and preventing minimal and major brain damage.

Proposed course: If we find that following frank encephalitis with a given virus there are no patterns or serious sequelae in the overwhelming majority of patients, this study will be abandoned. If not, we will pursue any leads we discover.

Honors and Awards: None

Publications: Brody, J. and Wilner, E.; Measles, Minor Neurologic Signs and Intelligence, Developmental Med. and Child Neurol., (In press).

Serial No. NDS (CF) - 68 E 1593
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The prognosis of general paresis after penicillin treatment

Previous Serial Number: Same

Principal Investigator: Elliot C. Wilner, M.D.

Other Investigator: Jacob A. Brody, M.D.

Cooperating Unit: St. Elizabeth's Hospital, Washington, D.C.

Man Years:

Total:	0
Professional:	0
Other:	0

Project Description:

Objectives: To determine if there is a difference in the prognosis of general paresis after treatment with penicillin compared with other forms of treatment.

Methods employed: One hundred patients at St. Elizabeth's Hospital diagnosed as having general paresis, and who satisfied our criteria of having been treated for the disease at least 10 years previously, comprised our study population. Patients were divided into three groups according to whether they were treated with penicillin alone, penicillin and malaria, or malaria or other unspecified treatment. Charts of the patients were then reviewed for evidence of neurological signs which developed only subsequent to treatment and which had no clear or likely cause other than progression of neurosyphilis. No attempt was made to evaluate any mental or neurological signs which were present before therapy. In each case, the type and amount of treatment for general paresis, as well as the results of serological and spinal fluid examinations were recorded.

Major findings: Gross evidence of progression of neurosyphilis appeared in 31 patients, whose average age was 53.1 years and average interval after treatment was 12.1 years. Among the various treatment groups the "malaria or other" patients had the lowest frequency of progression, 17% which probably implies that time had selected them as the most stable cases from among a much larger number of patients. Evidence of progression appeared in 39% of all those who received penicillin. There was not a tendency toward a lower frequency of progression among patients receiving higher

doses of penicillin. Progression usually occurred without reactive changes in the spinal fluid, and conversely, reactive changes in the spinal fluid did not always presage clinical progression.

Significance to biomedical research and the program of the Institute: The conclusion reached was that many of the neurologic complications occurring late in the course of treated general paresis probably reflect irreversible changes sustained before treatment, and it is unlikely that penicillin or any other treatment can completely prevent progression of the disease.

Proposed course: This project has been completed.

Honors and Awards: None

Publications: Wilner, E. and Brody, J.A.: The prognosis of general paresis after penicillin treatment. Lancet, 2:1370, 1968.

Serial No. NDS (CF) - 68 E 1594
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Phenothiazine-induced extrapyramidal disorders in twins with nonorganic psychoses

Previous Title: The frequency of extrapyramidal and lower motor neuron disease in demented patients

Previous Serial Number: Same

Principal Investigator: James A. Schnur, M.D.

Other Investigator: Jacob A. Brody, M.D.

Cooperating Units: Section on Twin and Sibling Studies, NIMH
National Research Council
National Academy of Sciences
Veterans Administration

Man Years:

Total:	1/2
Professional:	1/2
Other:	0

Project Description:

Objectives: To define the role of genetic influence in the production of phenothiazine-induced extrapyramidal disorders.

Methods employed: The study group is comprised of approximately 12-18 twin pairs, identical and fraternal, and approximately 24 sibling pairs. All subjects have the diagnosis of a nonorganic psychosis such as schizophrenia, and are on treatment with phenothiazines. Zygosity of the twins will be established by history, comparison of photographs and blood typing. Neurological examinations will be performed on each subject with particular attention paid to the presence or absence of the two most distinctive and readily identifiable phenothiazine-induced extrapyramidal disorders: lingual-oral-facial dyskinesia, with or without limb chorea, and a parkinson-like state. Using fraternal twins and sibling pairs as controls, we will determine whether the similar genetic constitutions of identical twins have a specific influence on the production and nature of extrapyramidal disorders in these subjects.

Major findings: To date three twin pairs have been examined. No conclusions have yet been drawn.

Significance to biomedical research and the program of the Institute: This work may lead to a better understanding of the etiology and treatment of phenothiazine-induced dyskinesia and parkinsonism.

Proposed course: Examinations of the remaining twin and sibling pairs are now in progress. This phase of the project should be completed within the next six months. Publication is anticipated during the next year.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1595
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: An evaluation of the effect of successful thalamic surgery on the progress of unilateral Parkinson's Disease

Previous Serial No.: Same

Principal Investigators: R. Michael Scott, M.D.
Jacob A. Brody, M.D.
Joyce M. Cannon, R.N.

Other Investigators: Irving S. Cooper, M.D.
St. Barnabas Hospital
Robert S. Schwab, M.D.
Massachusetts General Hospital

Cooperating Units: Department of Neurosurgery, St. Barnabas Hospital
Bronx, New York
Department of Neurology, Massachusetts General Hospital,
Boston, Massachusetts

Man Years:

Total:	1
Professional:	11/12
Other:	1/12

Project Description:

Objectives: To evaluate Dr. Cooper's hypothesis that in patients with unilateral Parkinson's disease, thalamic surgery which succeeds in permanently abolishing the tremor and rigidity on the involved side will either stop or markedly delay the appearance of the symptoms on the other side of the body; and to determine the natural history of unilateral Parkinson's disease.

Methods employed: The charts of 1,700 consecutive thalamic surgical cases from January, 1963 through September, 1964 at St. Barnabas Hospital were reviewed to select 100 patients who came to surgery with symptoms of tremor and rigidity confined to one side of the body. Seventy-two patients were eventually contacted and examined. Two unoperated groups were studied. The first of these consisted of 15 patients who presented to Dr. Cooper with unilateral signs, who were accepted for surgery, but for various reasons were not operated upon. The second control group consisted of 20 patients seen by Dr. Schwab in Boston and subsequently treated medically.

Major findings: Successful thalamic surgery does not affect the progress of tremor and rigidity to the extremities of the opposite side of the body. The rate and frequency of spread in unoperated and operated patients were strikingly similar. Certain of these patients had a form of Parkinson's disease characterized by unilateral tremor and rigidity of long duration. The average age of onset of these patients was earlier than that of "classical" Parkinson's disease patients, and they had a higher frequency of encephalitis or severe febrile illness prior to the onset of their illness. Thalamotomy was often extremely effective in these patients.

Significance to biomedical research and the program of the Institute: This study further defines the role of surgery in Parkinson's disease. It emphasizes that thalamotomy does not alter the course of progressive Parkinson's disease, but can restore to normalcy certain patients with the benign unilateral syndrome. In addition, it suggests ways in which patients with the benign syndrome might be identified.

Proposed course: Publications are being prepared.

Honors and Awards: None

Publications: Cooper, I.S., and Scott, R.M.: The clinical and physiological implications of 10 year cure of unilateral movement disorders by thalamic surgery. In: Proceedings of the IIIrd Parkinson's Symposium. Edinburgh, Livingstone, (in press).

Serial No. NDS (CF) - 68 E 1596
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Toxoplasma antibody in astrocytoma patients

Previous Serial No.: Same

Principal Investigators: R. Michael Scott, M.D.
Jacob A. Brody, M.D.

Other Investigators: None

Cooperating Units: The Departments of Neurosurgery at
Temple University, Philadelphia
University of Pennsylvania, Philadelphia
The Johns Hopkins University, Baltimore
National Naval Medical Center, Bethesda
Georgetown University, Washington, D.C.
Montefiore Medical Center, New York

Man Years:

Total:	1/2
Professional:	1/2
Other:	0

Project Description:

Objectives: To determine (1) whether astrocytoma patients have significant serum toxoplasma antibody; (2) whether the antibody is related to the histologic grade of the tumor.

Methods employed: Schuman et al., (Amer J. Pub Health 57:848-856, 1967) noted the association of CNS astrocytomas and toxoplasma antibody; however, their cases were not broken down into grades. This paper was of particular interest to us in that gliomas have been experimentally produced in chickens by innoculations of toxoplasma (Erichsen, S. and Harboe, A.: Acta Path. et Microbiol. Scandinav. 33:381-386, 1953). Therefore, we are obtaining serum specimens from patients with astrocytomas of all grades, postulating that the lower grade, cystic astrocytomas may have resulted from toxoplasma infection.

Major findings: 80 specimens have been collected and analyzed for toxoplasma antibodies. Only 3 samples show significant elevations.

Significance to biomedical research and the program of the Institute: The association of elevated toxoplasma antibodies with brain tumors of the astrocytoma type has not been verified. The three significant elevations of titer, however, were found in patients with "benign" type I tumors; it is possible that certain of these cases represent protozoan-induced tumors.

Proposed course: The data are being prepared for publication.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1597
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neurologic diseases in the Trust Territories and Other Pacific Areas

Previous Title: Hyperreflexia and spastic paralysis among New Caledonian lepers

Previous Serial Number: Same

Principal Investigators: Jacob A. Brody, M.D.
Edward W. Brink, M.D.
NINDS Research Center

Other Investigators: Manuel Cruz
NINDS Research Center
Jose Torres
NINDS Research Center
Francisco Leon Guerrero
NINDS Research Center

Cooperating Units: Department of Public Health, Trust Territory of the Pacific Islands, Saipan, Mariana Islands
Population Genetics Laboratory, University of Hawaii, Honolulu, Hawaii

Man Years:

Total:	0
Professional:	0
Other:	0

Project Description:

Objectives: To investigate neurologic illness occurring in the Trust Territories and the Pacific area. Last year this involved the study of leprosy patients in New Caledonia. This year it involved the study of congenital blindness among the people of Pingelap.

Methods employed: A field trip was made to Ponape to examine the Pingelapese people in order to document the nature of their eye disease and their mode of inheritance and epidemiologic patterns which could suggest both genetic and environmental factors.

Major findings: The congenital eye disease is apparently a form of tapetoretinal degeneration characterized by mystagmus, blinking, and photophobia, blindness, marked defect in color vision, and the development of cataracts usually within the first 5 to 10 years of life. The disease is nonprogressive, except for increasing visual difficulties as a result of the cataracts. The mode of inheritance appears to be recessive and nonsex-linked. A potentially important observation was that the Pingelapese population in the village of Mand had a much lower rate of blindness among children below age 5. This could be an artifact but also could imply that the gene which causes the blindness requires an external environmental factor in order to produce the symptoms.

Significance to biomedical research and the program of the Institute: The group of diseases which are included under tapetoretinal degenerations are poorly understood. By having a population isolate with a phenomenally high rate (10% of the population is blind) will give a unique opportunity for studying the full range of manifestations of this entity as the expression of a single abnormal gene. In addition, hopefully, a mechanism for prevention will develop.

Proposed course: We plan to follow the population to see if the pattern of manifestations change as the geographic localization of patients changes. In addition we will attempt to have several of the patients brought to NIH for more detailed studies using sophisticated equipment available here.

Honors and Awards: None

Publications: Brody, J.A., Yase, Y., Chemier, G., and Philippe, Y.: Hyperreflexia and spastic paralysis among New Caledonian lepers. Amer. J. Trop. Med. Hygiene 18:132, 1969.

Serial No. NDS (CF) - 68 E 1598
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Epilepsy on Guam

Previous Serial Number: Same

Principal Investigator: Edward W. Brink, M.D.
NINDS Research Center

Other Investigators: Jacob A. Brody, M.D.
Manuel Cruz
NINDS Research Center
Jose Torres
NINDS Research Center
Francisco Leon Guerrero
NINDS Research Center

Cooperating Unit: NINDS Research Center, Agana, Guam

Man Years:

Total:	1/2
Professional:	1/4
Other:	1/4

Project Description:

Objectives: To determine the incidence and prevalence of epilepsy on Guam. To investigate methods for field studies of epilepsy. To determine if previous reports of unusually high incidence of convulsive disorders on Guam are accurate.

Methods employed: We are testing four basic approaches: (1) we are following-up a 1962 survey of convulsive disorders in Umatac and Merizo to determine the outcome of those children known to have had febrile convulsions 6 to 8 years ago; (2) to determine the true incidence and prevalence in a sample population we are doing a house to house survey in the villages of Talofofo, Merizo, and Yona; (3) as referral neurologists on Guam we are updating all previous referrals of convulsive disorders to us and establishing a registry. To add to this registry we are contacting all medical and paramedical personnel on Guam to discover new cases. This registry will be permanent and permit us to conduct studies in the Guam population; (4) to further elaborate on methods for acquiring information we are following-up all births on Guam in 1958 and 1963 throughout the entire island to determine the rates of convulsive disorders in these preselected populations.

Major findings: We have already published that the rates of "true" epilepsy and of febrile convulsions are higher on Guam than elsewhere. We are completing the first three phases of the Epilepsy Study outlined in previous reports. We will have the information on the rate of "true" epilepsy (the fourth part of our program) and the establishment of a permanent Epilepsy Registry on Guam. There seems little doubt that the rates are high on Guam, but the reasons are not clear. Analysis of these data should be completed by July 1969.

Significance to biomedical research and the program of the Institute: Further studies of epilepsy in a well defined and accessible population will add to the understanding of this disease and contribute new information concerning epilepsy in a tropical environment. It will also yield important information on different survey techniques and their relative accuracy.

Proposed course: The data will be analyzed as soon as it is available and more detailed studies of epilepsy will develop from our basic information.

Honors and Awards: None

Publications: None

Serial No. NDS (EB) - 68 E 1599
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Relation of environmental and social factors to vascular disease mortality in Washington County, Maryland

Previous Serial No.: Same

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: George Comstock, M.D.
Johns Hopkins

Cooperating Unit: Johns Hopkins School of Hygiene and Public Health
Training Center for Public Health Research,
Hagerstown, Maryland

Man Years

Total:	1/6
Professional:	1/12
Other:	1/12

Project Description:

Objectives: The objective of this study is to determine the relationship between selected environmental and social factors in the subsequent occurrence of death from strokes and other major vascular diseases.

Methods employed: The study consists of relating data collected by the Johns Hopkins School of Hygiene and Public Health Training Center for Public Health Research in a 1963 census of Washington County to data on death certificates in the three following years. The census data are available on data processing cards. The study, therefore, consists of transferring the mortality data to electronic tape, editing the tapes, designing tables, and analyzing the results.

Major findings: None

Significance to biomedical research and the program of the Institute: Relating the occurrence of strokes to such factors as marital status, education, cigarette smoking, and other environmental factors may provide suggestions to etiology. Comparison of factors associated with strokes and factors associated with other major vascular diseases such as

Myocardial infarction may throw additional light on the etiology and prevention of strokes.

Proposed course: Preliminary runs are now available which indicate the frequencies of the variables of interest both in the census data and in the mortality data. Study is being completed at NIMH. It is anticipated that a final report should be available by the end of 1969.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1600
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Development of techniques for epidemiologic study of convulsive disorders

Previous Serial No.: Same

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigators: J. Kiffin Penry, M.D.
Section of the Epilepsies, C&FR, NINDS
R. Michael Scott, M.D.
Jacob A. Brody, M.D.

Cooperating Units: Section on the Epilepsies, C&FR, NINDS
Department of Preventive Medicine, College of Medicine, Howard University, Washington, D.C.

Man Years

Total:	5/12
Professional:	1/4
Other:	1/6

Project Description:

Objectives: The object of this study is to develop techniques for the epidemiologic study of convulsive disorders in different populations.

Methods employed: The assumption is made that the tendency toward convulsive disorders is a continuum in the general population. A questionnaire was developed to elicit a history of those symptoms clinically suspected of being common among those with convulsive disorders. The questionnaire was tested on two populations: a population of approximately 100 known epileptics from Children's Hospital and a second population of approximately 100 children born in 1962 at Freedmen's Hospital, Washington, D.C. The questionnaires were mailed by Howard University, College of Medicine, to the parents of all those children.

Major findings: The questionnaire succeeded in every case of known convulsive disorder in making the diagnosis properly. Of the 22 respondents from the Freedmen's Hospital population, 13 had one or more positive answers to the symptom questions. These are currently being examined to determine the significance to the positive responses.

Significance to biomedical research and the program of the Institute: Epidemiologic studies of epilepsy to date have been able to utilize only diagnoses made by practicing physicians in a given community. For this reason, they have been completely dependent upon the quality of medical diagnosis in the given community. This dependence has limited the opportunity to make comparisons of epilepsy prevalence in different populations. If it is possible to develop a technique for measuring comparably the prevalence of symptoms related to convulsions, it should be possible to do epidemiologic comparisons in a variety of populations. Such epidemiologic studies would then be able to indicate factors related to the occurrence of convulsive disorders and possibly suggest methods for their prevention.

Proposed course: Neurological examinations have been conducted on about 6 positive cases from the Freedmen's Hospital normal population. These were adequate to indicate only that there were no gross misinterpretations of the questionnaire. A report on the results of the pretest, being written at NIMH, should be completed by June 1969.

Honors and Awards: None

Publications: None

Serial No. NDS (EB) - 68 E 1601
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The epidemiology of convulsive disorders in Washington County, Maryland

Previous Serial No.: Same

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: J. Kiffin Penry, M.D.
Section on the Epilepsies, C&FR, NINDS

Cooperating Units: Johns Hopkins School of Hygiene and Public Health
Training Center for Public Health Research,
Hagerstown, Maryland
Washington County Health Department, Hagerstown
Section on the Epilepsies, C&FR, NINDS

Man Years:

Total:	1/4
Professional:	1/6
Other:	1/12

Project Description:

Objectives: The objectives of this study are to determine the relationships between selected environmental and social factors and the prevalence of convulsive disorders in Washington County; to demonstrate the feasibility and significance of new epidemiologic techniques for the investigation of convulsive disorders; and to determine the degree to which convulsive disorders are undiagnosed in a community.

Methods employed: Records of all cases of convulsive disorders in the County Clinic at Hagerstown will be abstracted. In addition, all practicing physicians in Washington County will be asked to give the name, address, and other identifying data on their patients who have convulsive disorders. These cases will represent the known patients with convulsive disorders in the community. Cases of all ages will be included in this survey. In a second survey, a screening questionnaire will be mailed to the parents of all children in the 3rd grade of school. For nonrespondents to the questionnaire, telephone interviewing and home visits will be made. It is anticipated that approximately 2,000 children will be surveyed. Using the questionnaire, 100 children with the greatest number of positive responses, 100 children who are completely negative, and 100 children from the intermediate group will be selected for

follow-up physicial examinations which will include a detailed neurological examination and electro-encephalogram.

Major findings: None

Significance to biomedical research and the program of the Institute: Demonstration of a feasible method to study the epidemiology of convulsive disorders in populations which may vary in their medical coverage will permit the investigation of epilepsy in many different communities and make it more likely that significant etiologic factors may be discovered. The study also should produce some substantive information on factors associated with the development of convulsive disorders, and should provide a very rough estimate of the degree to which convulsive disorders may be unrecognized in a community.

Proposed course: This study has been cleared by the Bureau of the Budget, but is awaiting contract approval. Major delays have been encountered in contract clearance, and alternative arrangements with NIMH are being explored. It is estimated that the study may begin in September, 1969. Physical examinations of the 300 children should be completed by the following summer.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1602
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Comparative epidemiology of major vascular diseases

Previous Serial Number: Same

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigators: None

Cooperating Unit: None

Man Years

Total:	1/3
Professional:	1/4
Other:	1/12

Project Description:

Objectives: The objective of this study is to determine the association of strokes with a number of demographic factors, utilizing data that have been collected by others, but not analyzed. A secondary objective is to indicate the kinds of epidemiologic data that are presently in greatest need.

Methods employed: Data have been collected from published and unplublished sources and are being analyzed using recently developed epidemiologic techniques which related prevalence of conditions in the living population to prevalence in decedents.

Major findings: The first subject analyzed in this study is the effect of sex on the prevalence of the major vascular diseases. Sex has been chosen as the first variable because of the striking difference in male/female ratios between coronary artery disease and strokes. Preliminary findings suggest that hemorrhagic strokes closely resemble hypertensive disease in their epidemiologic patterns and that thrombotic strokes closely resemble coronary disease.

Significance to biomedical research and the program of the Institute: Clarification of the relationship of strokes to other major vascular diseases should give us a better understanding of the causation of strokes. If it can be shown, for example, that thrombotic stroke deaths have similar associations as coronary disease deaths, then programs directed at preventing coronary disease may have similar effects upon thrombotic strokes. Similarly, programs

to control hypertension may be able to reduce considerably hemorrhagic stroke mortality.

Proposed course: Because of transfer of investigator to NIMH, this project is under review and may be discontinued.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1603
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Familial patterns of convulsive disorders during the first year of life

Previous Serial No.: Same

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: None

Cooperating Unit: Perinatal Research Branch, C&FR, NINDS

Man Years:

Total:	1/12
Professional:	1/24
Other:	1/24

Project Description:

Objectives: The objective of this study is to determine the degree to which convulsive disorders may be genetically determined.

Methods employed: Data collected in the Perinatal Research Project are being analyzed to determine whether the immediate relatives of infants with convulsive disorders have a greater prevalence of convulsive disorders than the immediate relatives of nonconvulsive infants.

Major findings: None

Significance to biomedical research and the program of the Institute: Determination of the degree to which epilepsy or convulsive disorders are familial should have an important influence on methods for control and prevention of the disease, and should give additional information on its etiology.

Proposed course: Tables have been designed and requested. Despite repeated requests, no data have been received and it must be assumed that work load has prevented the accomplishment of this work. Should the tables arrive, a report would require about three months to complete.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1604
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Oral contraception and US mortality rates

Previous Serial No.: Same

Principal Investigators: Robert E. Markush, M.D., M.P.H.
Daniel G. Seigel, M.D.
NICHD

Other Investigators: None

Cooperating Unit: National Institute of Child Health and Human Development

Man Years:

Total:	1/12
Professional:	1/24
Other:	1/24

Project Description:

Objectives: To determine whether oral contraceptives have had a detectable effect upon mortality rates among women in the US, and to determine which diagnostic categories may have been affected.

Methods employed: Only mortality data already available are being used. The data are obtained from the National Office of Vital Statistics. Much of the data is available in unpublished form. Mortality trends are being analyzed for specific diagnoses and specific age and six groups. Differences in the trends between males and females, and between females within the child-bearing ages and outside the child-bearing ages, will be noted and interpreted in light of the usage pattern of oral contraceptives.

Major findings: There have been increases in US mortality rates for venous and pulmonary thrombo-embolism that are compatible with case-control studies indicating an eight-fold increased risk of death from these causes associated with oral contraceptive usage. Findings are equivocal for coronary thrombosis, and negative for stroke.

Significance to biomedical research and the program of the Institute: The use of available mortality data is not a strong method for evaluating the influence of oral contraceptives upon mortality. Positive findings, however, suggest the need for more definitive studies. Because oral contraception is so widely used, it is important to determine its safety and its effect

upon health. Among the side effects suspected of association with oral contraceptives are a series of thrombo-embolic phenomena of which cerebral thrombosis and pulmonary embolism are perhaps the most serious. Epidemiologic studies already have indicated wide variation among populations in mortality from thrombo-embolic disease. It is, therefore, possible that different populations may have different reactions to the use of oral contraception. Although a moderate amount of data are available on the effect of oral contraceptives in England, data for the US are still very inadequate.

Proposed course: The study has led to several new projects, but is itself completed.

Honors and Awards: None

Publications: Markush, R.E. and Seigel, D.G.: Oral contraceptives and mortality trends from thrombo-embolism in the United States. J. Amer. Pub. Health Assoc. 59:418-434 1969.

Seigel, D.G. and Markush, R.E.: Oral contraceptives and relative risk of health from thrombo-embolism in the United States. Amer. J. Epid. (in press).

Serial No. NDS (CF) - 68 E 1605
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Phenothiazine-induced parkinsonism in white and Negro patients with nonorganic psychoses

Previous Title: Parkinsonism and skin pigmentation

Previous Serial Number: Same

Principal Investigators: James A. Schnur, M.D.
R. Michael Scott, M.D.

Other Investigators: Jacob A. Brody, M.D.

Cooperating Units: Spring Grove State Hospital, Catonsville, Md.
Crownsville State Hospital, Crownsville, Md.

Man Years:

Total:	2/3
Professional:	1/2
Other:	1/6

Project Description:

Objectives: To determine whether increased skin pigmentation is associated with decreased prevalence of phenothiazine-induced parkinson-like syndromes.

Methods employed: This project was originally designed to investigate influence of skin pigmentation on the prevalence of naturally occurring Parkinson's disease by use of a questionnaire which was to be mailed to a sample of American physicians. A pilot study, however, showed this approach to be impractical, and it was therefore abandoned. In view of the possible relationship between drug-induced and naturally occurring parkinsonism, we then decided to study comparable white and Negro populations who were on treatment with phenothiazines. Thus far, we have examined approximately 75 patients in each group, samples sufficient in number for a comparative analysis.

Major findings: Our initial results suggest that there is probably no difference in the prevalence of phenothiazine-induced parkinsonism between the two populations surveyed.

Significance to biomedical research and the program of the Institute: To further define the relationship between melanogenesis in the skin and in the pigmented nuclei of the basal ganglia.

Proposed course: Analysis of data is now in progress. Publication is anticipated during the next fiscal year.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1606
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Birth weight and economic status among Negros

Previous Serial No.: Same

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: None

Cooperating Units: Freedmen's Hospital
Department of Preventive Medicine, College of Medicine
Howard University

Man Years

Total:	1/6
Professional:	1/8
Other:	1/24

Project Description:

Objectives: To determine whether the lower birth weights generally found among Negroes can be explained by their lower economic status.

Methods employed: A comparison of birth weights will be made between children born to private and nonprivate patients at Freedmen's Hospital.

Major findings: None

Significance to biomedical research and the program of the Institute: Freedmen's Hospital contains a larger proportion of middle income Negroes than is generally available. Should it be found that lower birth weights among Negroes are primarily the result of economic factors, any attempt to increase Negro birth weights would need to be directed against these economic, not genetic, factors. Any influence of lower birth weight on the incidence of neurological disorders would then be understood as an economic one.

Proposed course: Final tables have been received after data processing. Analyses and final report have been delayed because of transfer of Principal Investigator to NIMH. Expected date of final report is October, 1969, depending, however, on availability at NIMH of necessary calculating equipment.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 1607
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Hypertension and strokes among telephone workmen

Previous Serial No.: Same

Principal Investigators: Robert E. Markush, M.D., M.P.H.
George Comstock, M.D.
Johns Hopkins University School of Hygiene and Public Health Training Center for Public Health Research

Other Investigators: None

Cooperating Units: Johns Hopkins University School of Hygiene and Public Health Training Center for Public Health Research, Hagerstown, Maryland
New York Telephone Company

Man Years

Total:	1/6
Professional:	1/12
Other:	1/12

Project Description:

Objectives: To determine the relationship between blood pressure level and the subsequent development of stroke and myocardial infarction.

Methods employed: In 1963, about 1,500 telephone workers were examined. Examination included EKG, blood pressure, and interview for cardiorespiratory symptoms and cigarette smoking. These same men are being examined in 1968; in addition, their health records are being reviewed to determine rates and causes of illness and death.

Major findings: None

Significance to biomedical research and the program of the Institute: Determination of the role of hypertension, smoking, heart disease and other factors in subsequent strokes should help in understanding the etiology and prevention of this major cause of death.

Proposed course: Because of Telephone Company strikes, the follow-up examinations have been indefinitely postponed. Study has been discontinued.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1608
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Evaluation of the importance of common neurological conditions to mortality

Previous Serial No.: Same

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: None

Cooperating Unit: Johns Hopkins School of Hygiene and Public Health
Training Center for Public Health Research
Hagerstown, Maryland

Man Years

Total:	1/12
Professional:	1/12
Other:	0

Project Description:

Objectives: The objective to this study is to determine the true association with mortality of neurological conditions independently from diagnoses collected from death certificates.

Methods employed: A method has been developed to measure the statistical association with mortality for any disease or factor, without use of death certificate data. The method requires data on prevalence of conditions in life and at death. Prevalence in life has been determined through epidemiologic surveys; prevalence at death can be determined through several techniques, one of which has been applied in a pilot study of 507 deaths. By appending a brief disease check list to death certificates in Washington County, Maryland, more definitive data will be collected for a specific community.

Major findings: Pilot study data have suggested that strokes are somewhat more significant as a cause of death than indicated by underlying cause statistics, that myocardial infraction is considerably overestimated by the underlying cause statistics, and that hypertension may be considerably more important.

Significance to biomedical research and the program of the Institute: More accurate measurement of the effect of conditions on community mortality

should provide a powerful epidemiologic tool for determing the distributions of the more common neurological conditions, particularly those which rarely appear on death certificates.

Proposed course: Study will continue in collaboration with NIMH. It is planned to begin collection of data late in 1969. After data have been collected for one year, the first report will be prepared.

Honors and Awards: None

Publications: Seigel, D.G. and Markush, R.E.: Prevalence at Death. II. Methodological considerations for use in mortality studies. Amer. J. Pub. Health (in press).

Serial No. NDS (CF) - 68 E 1609
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individaul Project Report
July 1, 1968 through June 30,1969

Project Title: Prevalence of autopsy-determined vascular disease of heart and brain among medicolegal deaths in Dade County, Florida

Previous Serial No.: Same

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: John Feegel, M.D.
Medical Examiner

Cooperating Units: Dade County Medical Examiner's Office, Florida
Injury Control Program, National Center for Urban and Industrial Health, BDPEC, PHS, DHEW

Man Years

Total:	1/12
Professional:	1/24
Other:	1/24

Project Description:

Objectives: (1) To determine the prevalence of vascular disease of the heart and brain in accidental homicidal, and suicidal deaths over age 35; (2) to determine how the prevalence of vascular disease in the brain relates to vascular disease in the heart; and (3) to determine whether the degree to which the presence of vascular diseases of the heart and of the brain were associated with the manner of violent death.

Methods employed: A forensic pathologist has conducted or reviewed autopsies of all suicides, homicides, and motor vehicle deaths occurring in Dade County during July 1958 through June 1967. Findings pertaining to trauma, and other specific pathology in the lungs, heart, aorta, and brain, have been recorded in a standardized manner. The data will be processed and analyzed to meet the objectives specified.

Major findings: None

Significance to biomedical research and the program of the Institute: Because there is no way to measure atherosclerosis in living populations, resort must be made to autopsy populations to determine its prevalence. These populations are usually nonrepresentative because of selective factors

that lead to performance of autopsies on decedents. Although violent deaths are also selective and cannot represent the community's population, in many communities the fact that most violent deaths can be autopsied provides a potential means of comparing the prevalence of atherosclerosis in different populations if comparable methods are used. The first object of this study is therefore the demonstration of standardized methodology and the results of its application.

Vascular disease of the heart and brain have different population distributions, and it should be useful in determining why this occurs to compare their distributions within this study's subgroups.

The role that vascular lesions of the heart and brain may play in traumatic deaths, particularly motor vehicle deaths, has practical importance through the possibility of preventive programs. Comparing the prevalence of vascular disease in motor vehicle deaths who suffered potentially fatal injuries with their prevalence among suicide and homicide deaths of comparable ages and sexes may provide unique insight into whether vascular disease increases the risk of motor vehicle death.

Proposed course: All data collection has been completed. Coding has almost been completed. Because of several missing code sheets, and transfer of investigator to NIMH, there has been a delay in this project. It will, however, be completed at NIMH within the next year.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1610
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: National chronic respiratory mortality study

Previous Serial No.: Same

Principal Investigator: Robert E. Mirkush, M.D., M.P.H.

Other Investigator: None

Cooperating Units: None

Man Years

Total:	1/12
Professional:	1/12
Other:	0

Project Description:

Objectives: To evaluate the effect of chronic respiratory disease upon US mortality.

Methods employed: Data on presence and severity of chronic respiratory disease in decedents have been collected by mail from about 3,000 certifiers of US deaths.

Major findings: The contribution of these diseases to US mortality is considerably more than published mortality statistics suggest.

Significance to biomedical research and the program of the Institute: The importance of these diseases to public health suggests that greater efforts should be made to control and understand them. Furthermore, published mortality statistics probably have no value in epidemiologic studies of chronic respiratory disease.

Proposed course: Tabulations have been completed and the final paper in the series should be completed by the end of 1969.

Honors and Awards: None

Publications:

Markush, R.E.: National chronic respiratory disease mortality study. I. Prevalence and severity at death of chronic respiratory diseases in the US, 1963. J. Chron. Dis. Vol. 21:129-141, 1968.

Markush, R.E.: National chronic respiratory disease mortality study. II. Mortality associated with persistent cough and phlegm in the US, 1963. J. Chron. Dis. (in press).

Serial No. NDS (CF) - 68 E 1611
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Motor vehicle accidents in the US (1906-1964) - mortality related to age group

Previous Serial No.: Same

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigators: John Clark
Injury Control Program
Rhona Leibel
Injury Control Program
Carolyn Adams
Injury Control Program
Ben Ryterband
Injury Control Program

Cooperating Unit: Injury Control Program, National Center for Urban and Industrial Health, BDPEC, PHS, DHEW

Man Years:

Total:	1/12
Professional:	1/24
Other:	1/24

Project Description:

Objectives: To investigate the trends in motor vehicle mortality specific for age.

Methods employed: Published and unpublished US mortality rates since 1906 have been graphically analyzed and interpreted.

Major findings: Motor vehicle mortality since 1906 has been rising for those under age one and those 15-24; most other age groups have shown declines, particularly the elderly groups. It is hypothesized that inexperience, concern for self-preservation, changes in traffic regulations and road and vehicle design, increased exposure, lower ability of the elderly to adjust to hazards, and improved medical care are among the factors responsible for the age-specific trends.

Significance to biomedical research and the program of the Institute: Analysis of mortality trends has suggested potentially valuable areas for

further research in the prevention of an extremely important public health problem. New hypotheses for causation and prevention of motor vehicle deaths must be consistent with post age-specific experience.

Proposed course: This study has been transferred with the investigator to NIMH.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1612
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Studies in epidemiologic survey methods

Previous Serial Number: Same

Principal Investigators: Robert E. Markush, M.D., M.P.H.
Daniel G. Seigel, M.D.
NICHHD

Other Investigators: None

Cooperating Unit: National Institute of Child Health and Human Development, NIH

Man Years:

Total:	1/12
Professional:	1/12
Other:	0

Project Description:

Objectives: To determine the influence of nonresponse on the results of epidemiologic surveys.

Methods employed: Nonrespondents to a mailed epidemiologic form were requeried. The results after requery were compared with the original results.

Major findings: Questions which yielded a greater proportion of positive responses had higher response rates. Persons whose responses eventually were negative to a given question were less likely to respond than persons whose responses were positive. The bias resulting from nonresponse was at a maximum for questions that were intermediate in their proportion positive.

Significance to biomedical research and the program of the Institute:

Proposed course: Study completed.

Honors and Awards: None

Publications: Seigel, D.G. and Markush, R.E.: The interpretation of incomplete responses to a mailed epidemiological inquiry. Arch. Environ. Health, 16:420-423, 1968.

Serial No. NDS (CF) - 68 E 1613
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Osteoporosis, fractures, and ethnic group in Jerusalem, Israel

Previous Serial Number: Same

Principal Investigators: Robert E. Markush, M.D., M.P.H.
Jacob Menczel, M.D.
Hadassah Medical Organization
Myer Makin, M.D.
Hadassah Medical Organization
Gordon Robin, M.D.
Hadassah Medical Organization
Donald G. Whedon, M.D.
NIAMD

Other Investigators: None

Cooperating Units: Hadassah Medical Organization, Jerusalem, Israel
National Institute of Arthritis and Metabolic Diseases, NIH
Injury Control Program, National Center for Urban and Industrial Health, BDPEC, PHS, DHEW

Man Years:

Total:	1/12
Professional:	1/12
Other:	0

Project Description:

Objectives: To determine how the prevalence of osteroporosis and the incidence of fractures relates to ethnic group, diet, and other environmental factors; and to determine which measures of osteroporsis relate most closely to fracture incidence.

Methods employed: A sample of the Jerusalem population is being examined for osteoporosis and followed over five years for fracture incidence.

Major findings: None.

Significance to biomedical research and the program of the Institute:

Determination of factors related to occurrence of osteoporosis should help in their prevention. Determination of measures capable of indicating risk of future fracture should help both in the understanding and in the prevention of fractures.

Proposed course: NINDS collaboration in this study has been discontinued.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1614
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The effect of seat belts in government motor vehicles

Previous Serial Number: Same

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigators: None

Cooperating Unit: Injury Control Program, National Center for Urban and Industrial Health, BDPEV, PHS, DHEW

Man Years:

Total:	1/24
Professional:	1/24
Other:	0

Project Description:

Objectives: To determine whether the installation of seat belts in government vehicles has been associated with a change in motor vehicle accident mortality rates.

Methods employed: A survey of government agencies was conducted to determine the timing and extent of seat belt installation. Accident records are to be correlated with the seat belt installation data.

Major findings: None

Significance to biomedical research and the program of the Institute: Although the method is unlikely to show an effect of the seat belts, since it is suspected that available belts have generally not been used, the demonstration of the lack of an effect should justify further efforts in either getting belts used or in determining why they have not been effective.

Proposed course: Transferred to NIMH.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1615
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Pilot study of viral antibodies in acute iridocyclytis

Previous Serial Number: Same

Principal Investigators: Richard E. Goldberg, M.D.
Frank H. Reuling, Jr., M.D.

Other Investigators: John L. Sever, M.D.
Perinatal Branch, NINDS
J. Theodore Schwartz, M.D.

Cooperating Units: Laboratory of Infectious Diseases, PRB, NINDS

Man Years:

Total:	0
Professional:	0
Other:	0

Project Description:

Objectives: To study the relationship between acute iridocyclytis and serologic evidence of previous or coexisting viral infection.

Methods employed: A series of cases experiencing first episode of acute iridocyclytis will be identified. Each patient will be matched with a control subject on the basis of age, race, sex and area of residence. Blood specimens for viral antibody determinations will be drawn on each case at the time of diagnosis and again 4 weeks later. Similar specimens will be obtained on the matched comparison group. Complement fixation studies will be undertaken with a series of 40 virus antigens. Antibody response among the case and control group will be compared for the initial specimens and for change in antibody level after 4 weeks.

This pilot study is being designed to obtain preliminary data on the frequency of selected antibodies among the study and comparison groups and to appraise the logistics related to acquisition of adequate specimens and clinical documentation for case and controls. The pilot phase will comprise a series of 25 cases and their comparison subjects.

It is proposed that patients be brought into the study through ascertainment in outpatient departments of Ophthalmology at Washington Hospital Center and USPHS Hospital, Baltimore, Maryland.

Major findings: None as yet.

Significance to biomedical research and the program of the Institute: The cause of acute iridocyclytis remains an enigma. Through this method of study it may be possible to identify viral agents worthy of more detailed study as possible causes of iridocyclytis.

Proposed course: The project was curtailed during the past year due to limited funds. It will be reconsidered when funds become available.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 68 E 1616
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Comparison of glaucoma suspects identified by different methods of tonometry

Previous Serial Number: Same

Principal Investigator: J. Theodore Schwartz, M.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	0
Professional:	0
Other:	0

Project Description:

Objectives: To determine the influence of variation in the method of tonometry on the selection of glaucoma suspects.

Methods employed: Data obtained in community-wide surveys previously undertaken by this Section were reanalyzed to identify and compare those individuals who were selected as positive screenees by different tonometric methods. Data from previous surveys at Nesquehoning, Penn. and Colorado River Reservation, Arizona were used in this study. In these surveys intraocular pressure of each examinee was measured by 3 different methods: Goldmann applanation in the sitting position, Goldmann applanation in the supine recumbent position, and Schiotz in the sitting position.

Major findings: At the critical screening level of 21 mm hg, slightly fewer than 1/3 of those individuals who were positive by any method were positive by all 3 methods. With regard to the more commonly employed method of tonometry, that is, Schiotz measurements and Goldmann applanation measurements taken in the sitting position, only half of the persons who were identified as positive screenees by either method were so classified by both. The extent of agreement in identifying positive screenees at the critical screening level of 25 mm hg was no better.

Significance to biomedical research and the program of the Institute: The extent of agreement among these tonometric procedures in selecting positive screenees was limited. The findings suggest the need for further investigation of the efficiency of tonometric screening for glaucoma.

Proposed course: This project is completed.

Honors and Awards: None

Publications: Schwartz, J.T.: Vagary in tonometric screening. American Journal of Ophthalmology 64: 1967.

Serial No. NDS (CF) - 68 E 1617
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Television Ophthalmoscopy

Previous Serial Number: Same

Principal Investigators: J. Theodore Schwartz, M.D.
C. A. Caceres, M.D.
NCHSR&D
R. L. Dallow, M.D.
NCHSR&D
Mark M. Wilburn
NCHSR&D

Other Investigators: None

Cooperating Unit: Medical Systems Development Laboratory
National Center for Health Services and
Research Development

Man Years:

Total:	1
Professional:	1
Other:	0

Project Description:

Objectives: To coordinate the development of an instrumentation system utilizing television ophthalmoscopy and electronic data processing.

Methods employed: The Section on Ophthalmic Field and Developmental Research and the Medical Systems Development Laboratory have entered into an agreement to undertake collaborative development of a practical instrumentation system utilizing television ophthalmoscopy and electronic data processing. Under this agreement the MSDL has (a) conducted a detailed analysis of the potential applications of TVO; (b) prepared, on the basis of the analysis, recommendations for optimal applications of a system of TVO and automatic data processing; and (c) prepared a plan for system development terms of cost and development time. The project is now being implemented. A critical evaluation of the quality of electronic signals which can be derived from selected clinical applications is the objective of the current phase of the project. Clinical trials for data acquisition and preliminary programming for automatic processing of the electronic signals will follow.

Major findings: No scientific findings to date.

Significance to biomedical research and the program of the Institute: Measurements such as circulation time, ophthalmogynamometry and glaucomatous cupping of the optic nerve head will be attempted. With successful development, applications of this modality hold promising value in mass screening programs, basic research and clinical practice.

Proposed course: This project is continuing.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 69 E 1774
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neurologic signs and symptoms associated with malabsorption

Previous Serial Number: None

Principal Investigator: Paul M. Hoffman, M.D.

Other Investigator: None

Cooperating Units: Central Veterans Administration Authority, Washington, D.C.
Veterans Administration Hospital, Atlanta, Georgia
Veterans Administration Hospital, Long Beach, California

Man Years:

Total:	1/2
Professional:	1/2
Other:	0

Project Description:

Objectives: To determine if both clinical and subclinical malabsorption is associated with a high incidence of neurologic signs and symptoms.

Methods employed: Hospital records of patients who had hemigastrectomies and vagotomies along with Billroth II type of reconstruction at the Atlanta Veterans Administration Hospital in the years 1952 through 1956 were reviewed. A group of 53 patients had a complete history taken by the principal investigator and then were given a complete neurological examination. Patients' records were reviewed at Long Beach Veterans Administration Hospital and patients who had vagotomies and pyloroplasties performed in the years 1952 through 1956 were chosen. Since these patients have normal absorption they are the controls. This group has been scheduled for the same type of evaluation in late May. A larger population study, using abstracts from an original 1500-case study of surgery for peptic ulcer disease has been undertaken. From the Veterans Administration Central Office claim numbers for each of these patients were obtained. From this claim number we can determine deaths within this group and death certificate data concerning this group will be obtained.

Major findings: In the hemigastrectomy group examined at Atlanta, 25 percent of the patients examined had signs and symptoms of nervous system disease ranging from sensory peripheral neuropathies without reflex changes to an apparent case of motor neuron disease. All of the patients within this group who had evidence of nervous system disease gave positive histories for the symptoms of malabsorption. Their average weight loss following surgery as compared to those without neurologic symptoms within this group was significantly higher. No information on the vagotomy and pyloroplasty group has yet been obtained.

Significance to biomedical research and the program of the Institute: There have been many clinical reports of cases of malabsorption who have shown signs and symptoms of nervous system disease. There have also been scattered reports in literature of patients who are known to have motor neuron disease, who had a history of having had a Billroth II type of gastric surgery performed many years prior to the onset of their disease. There has never been, however, a matched, controlled population study of the association of these two abnormalities. If this association is valid then further study into the mechanism of absorption of essential nutrients and their incorporation into nervous tissue may be a meaningful approach to the study of chronic neurologic disease.

Proposed course: This project will continue.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 69 E 1775
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Comparison of MS among Irish and Italian immigrants in New York City

Previous Serial Number: None

Principal Investigators: Joyce M. Cannon, R.N.
Jacob A. Brody, M.D.

Other Investigator: None

Cooperating Unit: National Multiple Sclerosis Society, New York, N.Y.

Man Years:

Total:	11/30
Professional:	1/5
Other:	1/6

Project Description:

Objectives: To determine if the rate of MS is changed among people migrating from an area of low incidence to a high risk area. Ireland has a high rate of MS while Italy has a low rate.

Methods employed: We plan to review death certificates from 1940 going back to 1920. During this time approximately 2,000 Italian born and 2,000 Irish born people died in Manhattan per year.

Major findings: None

Significance to biomedical research and the program of the Institute: It is known that populations migrating from high incidence areas of MS to low incidence areas retain the MS rate of country of birth suggesting that events early in youth (possibly infectious) cause MS. This study will provide the corollary data about migration from low to high risk areas.

Proposed course: Because of the magnitude of the task of reviewing this number of death certificates, we have appealed to the National Multiple Sclerosis Society for volunteers to do the tedious identification and abstracting work. They have been unsuccessful in producing volunteers to begin our pilot study of a five-year period, thus we must find a new source of manpower in order to complete this investigation.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 69 E 1776

1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Cerebrospinal fluid amines in drug-induced extrapyramidal parkinsonism-like disorders.

Previous Serial No.: None

Principal Investigator: James A. Schnur, M.D.

Other Investigator: Thomas N. Chase, M.D., N.I.M.H.

Cooperating Units: Unit on Neurology, N.I.M.H., Spring Grove State Hospital, Catonsville, Maryland
Crownsville State Hospital, Crownsville, Maryland

Man Years:

Total:	2/3
Professional:	1/2
Other:	1/6

Project Description:

Objectives: To study central nervous system amine metabolism in patients with drug-induced extrapyramidal disorders.

Methods employed: Spinal fluids of clinically defined cases of drug-induced extrapyramidal disorders are analyzed by conventional biochemical methods for amine metabolities.

Major findings: Preliminary results suggest that cerebrospinal fluid homovanillic acid and 5-hydroxyindoleacetic acid levels may correlate with akinesia and tremor respectively in patients with drug-induced extrapyramidal disorders and parkinsonism.

Significance to biomedical research and the program of the Institute: This work may lead to further understanding of the biochemistry--and treatment of these untoward drug reactions.

Proposed course: Data collection is nearing completion. Analysis is in progress. Publication is anticipated during the next year.

Honors and awards: None

Publications: None

Serial No. NDS (CF) - 69 E 1777
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: ALS among non-Chamorros after residence on Guam

Previous Serial Number: None

Principal Investigator: Jacob A. Brody, M.D.

Other Investigators: Renee C. Nelson, Program Analyst
Estelle Kornhauser, R.N.

Cooperating Unit: Bureau of Data Processing and Accounts
Social Security Administration
DHEW

Man Years:

Total:	1/2
Professional:	5/12
Others:	1/2

Project Description:

Objectives: This project was developed to determine if prolonged exposure (over one year) to the environment of Guam increases the likelihood of the development of ALS among statesiders.

Methods employed: Through various workers in the Department of Defense we were put in contact with several construction companies which had maintained large staffs of statesiders on the island of Guam after World War II. These companies were asked to supply us with the names, birthdates, and social security numbers of all personnel employed on Guam and from these lists we selected only those workers who had spent more than one year on Guam. This was a group of approximately 12,000 individuals. The Social Security Administration searched its records to determine which of these workers had died and where they had died. We are contacting the individual states to obtain the death certificates of the deceased workers and determine the cause of their death.

Major findings: Of the approximately 12,000 cards submitted to the Social Security Administration, 450 were found to contain incorrect information making follow-up impossible. 7,730 were considered as representing individuals still alive, and the remainder (4,000) were identified as to place of death. These names were submitted to the individual states and death certificates requested. About two-thirds of the requested certificates have been returned to date.

Significance to biomedical research and the program of the Institute: Although results on this study are far from complete, the initial trend is that the rate of ALS among statesiders who have spent considerable time on Guam remains the same as that for statesiders who have never spent time in that environment. If this trend is borne out by subsequent findings, it would suggest that the environmental factors on Guam are less likely to be responsible for high rate of ALS among its native population.

Proposed course: Further efforts are being made to locate death records on all individuals reported to us as having died. Perhaps a review of the living cases will be made to determine if any of them are suffering from ALS.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 69 E 1778
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Familial cortical cerebellar degeneration

Previous Serial Number: None

Principal Investigators: Paul M. Hoffman, M.D.
William H. Stuart, M.D.

Other Investigators: Roswell Eldridge, M.D.
Joyce M. Cannon, R.N.
Anne Harlan

Cooperating Unit: None

Man Years:

Total:	1/3
Professional:	1/6
Other:	1/6

Project Description:

Objectives: To determine the genetic pattern and the incidence of cortical cerebellar degeneration in a family in the northern Georgia section of the Blue Ridge Mountains.

Methods employed: A complete family history and a family tree will be obtained from the proband and his family who are now living in Hiawasee, Georgia. Affected members will be examined as well as those who are at risk but who have not shown the signs and symptoms of the disease. Hospital records and autopsy material, when available, will be collected.

Major findings: The proband is an 80-year-old white male who demonstrated abnormal finger to nose and heel to shin tests as well as inability to maintain his balance, and persistent truncal titubation. He also exhibited scanning-type of cerebellar speech for the last two years. There is no evidence of long-track involvement or of abnormalities in position or vibratory sensation. The reflexes were described as normal. Preliminary analysis of the data available indicate that this may be recessive form of inheritance in this particular family.

Significance to biomedical research and the program of the Institute: Hereditary spinocerebellar degeneration as well as hereditary cortical cerebellar degeneration have been described in literature as having dominant patterns of inheritance. The family under investigation show the rather unique type of cerebellar degeneration which has not previously been described in the hereditary syndromes. It also seems likely that this may be a recessive gene in this particular family.

Proposed course: This project will continue.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 69 E 1779
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The epidemiology of motor neuron disease in the United States

Previous Serial Number: None

Principal Investigators: Paul M. Hoffman, M.D.
Jacob A. Brody, M.D.

Other Investigator: Joyce M. Cannon, R.N.

Cooperating Units: Bureau of Disability Insurance, Social Security Administration
North Carolina State Department of Public Health
University of North Carolina School of Medicine
Duke University School of Medicine
Charlotte Memorial Hospital

Man Years:

Total:	11/12
Professional:	10/12
Other:	1/12

Project Description:

Objectives: 1. To determine if the diagnoses on death certificates are an adequate reflection of the incidence of motor neuron disease in the United States. 2. To determine if there has been a change in the epidemiology of motor neuron disease from that previously described. Specific parameters include duration of symptoms, geographic, racial, and socio-economic distribution.

Methods employed: Hospital records were reviewed on those patients who had a diagnosis of motor neuron disease in years 1958 through 1962 at the three North Carolina Hospitals. Death certificates were then obtained on those patients who had died in the state of North Carolina. Those patients who are still living were followed-up through the County Public Health Departments within the state of North Carolina and information was obtained on these patients. Through appropriate channels, demographic data concerning patients who had a diagnosis of motor neuron disease and were paid disability from 1958 to the year 1962 will be obtained.

Major findings: Of the death certificates obtained, the diagnosis of motor neuron disease appeared on 75 percent. Forty-two patients were followed-up by the Public Health Departments in North Carolina and information was obtained on 40 of these. This data is now being compiled. It was found that 20 percent of the patients with this diagnosis in North Carolina were alive at least 5 years with their disease and many for more than 10 years. Follow-up of these cases is now being initiated by Dr. Irwin Brody at Duke University Medical Center. Data from the Bureau of Disability Insurance is now being compiled.

Significance to biomedical research and the program of the Institute: Since most of the estimates of the prevalence of motor neuron disease are based on mortality reporting, we would like to know if mortality reporting is indeed an accurate method for ascertaining this information. We would also like to compare this method with the method of determining demographic data by the use of disability claims through the Social Security Administration. Both of these methods could prove to be useful in determining the epidemiologic patterns of amyotrophic lateral sclerosis in the United States. The investigation of the patients who have lived for longer than 5 years with their disease may lead to one or more of the following conclusions: (1) That there is an as yet undescribed syndrome of atypical motor neuron disease which has symptoms which last for many years longer than that described for classical ALS. (2) There is a great deal of misdiagnosis made with this syndrome. (3) That with more modern hospital facilities and better nutrition, or perhaps a shift in the nature of the disease, patients with classical ALS live for longer periods of time.

Proposed course: This project will continue.

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 69 E 1780
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Familial bilateral acoustic neuroma

Previous Serial Number: None

Principal Investigators: Dean F. Young, M. D.
Roswell Eldridge, M. D.

Other Investigators: Jane McNew, R. N.
W. J. Gardner, M. D.
Cleveland, Ohio
Joseph J. Adamkiewicz, M. D.
Johns Hopkins Hospital
George T. Nager, M. D.
Johns Hopkins Hospital
Frank H. DeLand, M. D.
Johns Hopkins Hospital

Cooperating Units: Department of Otolaryngology,
Department of Radiology,
Department of Neurosurgery,
Johns Hopkins Hospital
Baltimore, Maryland

Man Years:

Total:	3
Professional:	2
Other:	1

Project Description:

Objectives: To perform genetic, clinical and physiologic studies of a large family with hereditary bilateral acoustic neuroma.

To clarify the relationship of this trait to other disorders with acoustic disorders such as generalized neurofibromatosis.

Methods employed: Field studies were conducted in evaluating family members. On those seen personally, physical examinations were performed, stressing neurological and skin examinations. In addition, audiometric examinations including air and bone conduction and caloric examinations were conducted in the field.

Genealogic information was obtained from family members, family records, D.A.R. records, state and military records, census recordings. Medical history was obtained from family members, hospital and physician records, occasionally from school records or military records.

On select patients extensive outpatient studies have included audiometric and vestibular testing, complete ENT and neurologic examinations, skull x-rays and brain scans using radioactive techniques. These were undertaken in cooperation with the departments of neurology, radiology and otolaryngology of Johns Hopkins Hospital.

Major findings: More than 1000 family members have been ascertained. Of these 101 are felt to have definite or possible bilateral acoustic neuroma.

Clinical characteristics include: an average age of onset at 19 years; survival after onset of symptoms in unoperated cases averages 19 years with a range of two to 44 years. The initial symptoms are deafness in 52%, tinnitus in 33%, imbalance in 10%, and facial twitching in 5%. A decrease or absence in caloric response and/or diminished air and bone conduction are the earliest signs. Surgery, at least as performed in the past, has not been helpful.

The trait is autosomal dominant with virtually complete penetrance. It appears to be distinct from classical neurofibromatosis. Whether it is distinct from the "central form" of neurofibromatosis, which is associated with multiple CNS tumors, is less clear.

Results of outpatient examinations demonstrate clearly the lack of reliability of any single test in early diagnosis of these tumors. Early audiometric findings are variable and brain scan in relatively early diagnosis of the tumor seems useful.

Significance to biomedical research and the program of the Institute: The mode of inheritance of this trait has been confirmed and the place of this syndrome among those associated with neural sheath proliferation is clearer. Of primary importance is the establishment of appropriate diagnostic techniques for early cases and treatment of these cases.

Proposed course: Departments of Otolaryngology, Radiology and Neurosurgery of Johns Hopkins Hospital will investigate selected members of this family.

Honors and Awards: None

Publications: Young, D.F., McNew, J., and Eldridge, R.: Hereditary Acoustic Neuroma-Clinical and Genetic Aspects. In Transactions of the American Neurological Association. 94 (In press)

Serial No. NDS (CF) - 69 E 1781
1. Collaborative Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Twin Studies in Parkinson's Disease

Previous Serial Number: None

Principal Investigators: Roswell Eldridge, M. D.
Zdenck Hrubeck
National Academy of Sciences

Other Investigator: Anne Harlan

Cooperating Unit: The National Academy of Sciences-National Research Council Twins' Registry, Washington, D. C.

U. S. Veterans Administration
Washington, D. C.

Man Years:

Total:	1/4
Professional:	1/8
Other:	1/8

Project Description:

Objectives: Parkinsonism is not a single entity but rather a symptom complex which may be idiopathic, or may be due to cerebral arteriosclerosis or may follow encephalitis. Genetic factors have been considered important by a number of authors but it is not yet established how important such factors are in any one form of Parkinsonism or if there is a form which has a simple genetic basis independent of acquired neurologic disease. The aim of the present proposal would be to use the twin method to evaluate genetic factors in various forms of Parkinsonism and/or to distinguish genetically determined Parkinsonism from other forms.

Methods employed: Survey of the VA twin registry in 1968 has revealed eight cases of Parkinsonism, all of which are apparently discordant. Two were monozygotic, five were diozygotic and in one the zygosity was unknown. We would contact each of these individuals and his co-twin, and others with the diagnosis who may be ascertained through updating of the registry, and arrange for an appointment with the individual in his home at a time when available relatives could also be present. During the family interview a pertinent medical history would be obtained and physical examination would be performed. Permission for review of

hospital records would be secured and arrangements might be made for additional neurologic studies. To define zygosity, photographs would be taken of the twins, blood would be drawn for genotyping and dermatoglyphics might be recorded. (Personal examination of both twins and available relatives is important in order that mild cases not be missed).

Major findings: See "Methods Employed".

Significance to biomedical research and the program of the Institute: In a chronic condition with late onset it is often difficult to determine the role of genetic factors in causation. The twin method provides a relatively simple method involving small numbers to answer this question.

The nosology of Parkinson's Disease is especially important now that the drug L-dopa has been shown to help some with Parkinsonism. Is this drug most helpful in a specific form of the disease? Is it effective in hereditary Parkinsonism?

Proposed course: See "Methods Employed".

Honors and Awards: None

Publications: None

Serial No. NDS (CF) 69 E 1782
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1,1968 through June 30, 1969

Project Title: Twin Studies in Torticollis

Previous Serial Number: None

Principal Investigators: Roswell Eldridge, M. D.
Zdenck Hrubec
National Academy of Sciences

Other Investigators: Anne Harlan

Cooperating Unit: The National Academy of Sciences-National Research Council Twins' Registry, Washington, D. C.

U. S. Veterans Administration
Washington, D. C.

Man Years:

Total:	1/4
Professional:	1/8
Other:	1/8

Project Description:

Objectives: Torticollis may be broadly divided into infantile and post-infantile forms. The former may be congenital or appear several weeks after birth but in either the cause appears due to events preceding birth. Post-infantile torticollis consists of a heterogeneous group of disorders which have been ascribed to a number of causes including trauma or inflammation of the cervical spine, myositis of nuchal musculature, functional illness, and disease of the peripheral or central nervous system. In addition torticollis on an hereditary basis, either as an isolated symptom or in association with other movement disorders such as torsion dystonia, has been the subject of numerous reports. The aim of the proposed study is to weigh the genetic factors in the post-infantile forms of torticollis and, if possible, to distinguish between discreet hereditary types.

Methods employed: In 1968 a review of the Veterans Administration twin registry disclosed 11 individuals with a diagnosis of torticollis, all of whom were said to be discordant. Five were monozygotic, two were diozygotic and in the four the zygosity could not be established. We would contact each of these individuals and his co-twin, arrange for

an appointment with the individual in his home at a time when available relatives could also be present. (We would hope also to ascertain new cases by assisting in the up-dating of the twin registry). During the family interview the pertinent medical history would be obtained for all relatives and physical examination performed on those present. Permission for review of hospital records would be secured and arrangements might be made for additional neurologic studies. To establish zygosity, photographs would be taken of the twins, blood would be drawn for genotyping, and dermatoglyphics might be recorded.

Major Findings: See "Methods Employed".

Significance to biomedical research and the program of the Institute: Torticollis may be hereditary or acquired but under each of these headings there appear to be a number of discreet entities. The twin method presents a relatively simple means to distinguish genetically determined forms. Concentration on torticollis which is simply inherited is worthwhile since such disorders should have a discreet biochemical basis which might be revealed by study with the neurochemical techniques now available.

Proposed course: See "Methods Employed".

Honors and Awards: None

Publications: None

Serial No. NDS (CF) - 69 E 1783
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Heritability of the Effect of Corticosteroids on Intraocular Pressure

Previous Serial Number: None

Principal Investigator: Frank H. Reuling, M.D.

Other Investigators: J. Theodore Schwartz, M.D.

Cooperating Units: NAS-NRC Twin Panel

Man Years:

Total:	1 1/2
Professional:	1
Other:	1/2

Project Description:

Objectives: To assess the role of genetic factors in determining the intraocular pressure response caused by topical application of steroid eye drops. Other humoral and metabolic factors which may correlate with the steroid response will also be investigated.

Methods employed: A sample of 50 pairs of monozygous twins and 50 pairs of like sex dizygous twins over 15 years of age are being examined according to a standard protocol. Dexamethasone 0.1% eye drops are instilled three times per day for four weeks and the examination is repeated. Data is being gathered on family history of various diseases, various measures of intraocular tension before, during and after four weeks of steroids, and many anatomical observations such as gonioscopy, corneal thickness, cup/disk ratio are being recorded. In addition many blood chemistries including post prandial glucose and lipoprotein fractions are being obtained. Physical examinations are being performed by members of the Field Epidemiological Research Section of the N.H.I.

Major findings: None to date.

Significance to biomedical research and the program of the Institute:

If inheritance is found to play a major role in the transmission of the steroid response, this research would offer strong support for the need of further studies to define thoroughly the relationship between steroid responsiveness and chronic simple glaucoma. If inheritance is found not to play a significant role, the evidence would suggest the need to re-examine a popular hypothesis suggesting simple autosomal transmission of the hypertensive response to steroids. The efforts of two collaborating units, the Molecular Disease Branch of NHI and the Field Epidemiology Research Section of NHI who are conducting studies on the twins participating in this study, may, in addition to their own results, give some insight into the determinants of the steroid response.

Proposed course: This study will continue until 100 sets of twins have been tested. The protocol for this study was approved by the NSA-NRC Follow-Up Agency and they have granted us access to the twins in their Twin Panel who reside in the Washington-Baltimore metropolitan area. These twins will be used in addition to the twins in our twin panel. Analysis of data will await completion of the study.

Honors and Awards: None

Publications: None

HOW TO USE
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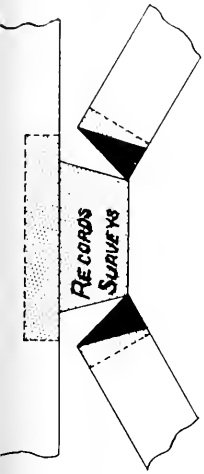

TABBED SEPARATOR SHEET
Form HEW-69
(3-56)

ANNUAL REPORT
July 1, 1968 through June 30, 1969
Special Projects Branch--Collaborative and Field Research
National Institute of Neurological Diseases and Stroke
National Institutes of Health

The Special Projects Branch is currently comprised of two broad-scale collaborative programs, one in head injury and one in epilepsy. Following a period of rapid expansion in FY 1967, these programs maintained their level of activity in FY 1968 and FY 1969. In April 1969, Dr. J. Kiffin Penry, Head of the Section on Epilepsy, assumed duties as Acting Chief of the Branch.

Section on Head Injury

During FY 1969 the Section on Head Injury has completed a field survey of head-injured veterans of the Korean Campaign, has continued the bioengineering research program aimed at the construction of physical and mathematical head models, and has begun a survey of current research in the field of head injury. Dr. Alex R. Taylor, visiting scientist and acting head of the section for one year, returned to his duties at the Royal Victoria Hospital, Belfast, Northern Ireland, at the end of October. Since then, Dr. J. Kiffin Penry, head of the Section on Epilepsy, has taken on the duties of acting head of this section as well.

A field survey of 876 head-injured veterans of the Korean Campaign and 121 matched controls was completed in February. Interviews with the veterans and their relatives and employers were carried out by the American National Red Cross Service to Military Families. Information was obtained on employment patterns over the past 15 years, the occurrence of post-traumatic symptoms, and the incidence of epilepsy in the veterans and their parents, siblings and children. The medical data were edited by the staff of the Section on Head Injury, while the National Research Council Follow-up Agency edited the socio-economic information and coded the interview schedules. These data, along with acute and previous follow-up data, were transferred to tape, and the analysis of the data has begun. Dr. Taylor has agreed to work with Mr. Seymour Jablon of the National Research Council Follow-Up Agency in the preparation of the final report. The Head Model Construction Committee has maintained an active interest and has made progress in defining specific information which must be determined by the contractors during Phase I.

In December 1968 the section began a comprehensive and in-depth survey of current research in head injury. Identification of investigators with programs in head injury research, and determination of the disciplines represented, institutions involved, specific areas of investigation, and the source, amount, and type of funding are the chief objectives of this effort. A comprehensive analysis of the programs in this field should aid in reducing duplication of effort and direct attention to those areas where additional support may be required. The diversity of governmental and nongovernmental agencies concerned with various aspects of head injury research accentuates the need for a program of this nature.

Section on Epilepsy

The activities initiated following the creation of the Section in fiscal year 1967 were continued and further developed by the same professional staff as in fiscal year 1968 and a greatly reduced supporting staff. Only because of the availability of part-time and temporary personnel has the Section been able to continue to function reasonably well.

The collection of data in the Collaborative Study of Epilepsy was completed 31December1968. Of the 172 patients admitted to study, all but 10 completed their scheduled follow-up examinations with 54 having been followed through the 22nd month examination. The principal investigators met in October, 1968, and discussed preliminary drafts of their manuscripts. The final retrieval of data was delayed due to a shortage of keypunch operators and programmers. However, all retrieval of data for primary tables and correlations have been completed so that the manuscripts and final reports are now in final draft.

The Section has continued its liaison with pharmaceutical companies having anticonvulsant drugs in varying stages of development. A considerable amount of pharmacological data and clinical information has been submitted and as a consequence, the Institute has knowledge of anticonvulsants under clinical evaluation in animal studies as those shelved by industry. At least 5 pharmaceutical companies have expressed an interest in our anti-convulsant drug program to aid in the development of new anticonvulsant agents.

New Castle State Hospital was awarded a $90,000 contract for anticonvulsant drug testing in late FY 1968. Virtually all of FY 1969 was required for "tooling up" at New Castle. Patients were selected as candidates for the trials; informed consent was obtained; an NINDS experimental design consultant made selections from this group and assigned patients to the study. The biochemist at New Castle has refined the gas chromatography technique for determining anticonvulsant drug blood levels of standard medications and developed a spectophotometric method for determining levels of the study drug, albutoin. This same period was required to prepare the medications to be employed in the double blind trials. Three pharmaceutical companies cooperated in providing drugs for the trial. Patient trials at New Castle began late in FY 1969 and will be completed late in FY 1970.

Two contracts were negotiated in June, 1969 to study certain effects of the anticonvulsant ethosuximide. The investigators are: Fritz E. Dreifuss, M.D., University of Virginia Hospital and Philip T. White, M.D., Marquette University School of Medicine. Two of the four investigators participated in the Institute's thirty month study, The Collaborative Study of Epilepsy. These new contracts will effectively utilize the skills and methodology developed by each investigator during his participation in the Collaborative Study of Epilepsy. Each investigator will study approximately 20 patients to determine information about reasons some patients fail to respond to ethosuximide, the drug of choice in the treatment of absence. Also, the effect of ethosuximide treatment on psychometric performance will be investigated and a more reliable assessment for the measurement of seizure frequency than the methods now available will be developed. Also, the

multicamera videotape techniques developed by this Section will be used for data collection in both studies. An additional benefit of this research is that it will provide future sources for clinical trial of new anticonvulsant drugs for the treatment of absence.

This year the director of the institute approved the creation of an Ad Hoc Committee on Anticonvulsant Drugs. This committee will:

1. Assist the Section on Epilepsy staff in developing broad program plans and establish priorities for the Institute's organized field research program on Anticonvulsant Drugs.

2. Review and advise the Section on contract proposals for directed research on anticonvulsant drugs prior to directorate and technical merit review by the Institute.

3. Advise the Institute on the status and merit of research on the anticonvulsant drug area; assist in the dissemination of information about the Institute's program and encouragement of research in the field.

Members of the Committee are: Richard P. Schmidt, M.D., Chairman (Professor of Medicine (Neurology), College of Medicine, University of Florida, Gainesville, Florida); James R. Fouts, Ph.D. (Professor of Pharmacology, College of Medicine, University of Iowa, Iowa City, Iowa); Merle L. Gibson, M.D. (Director, Division of Neuropharmacological Drugs, Food and Drug Administration, Arlington, Virginia); Glenn E. Ullyot, Ph.D. (Director, Scientific Liaison, Smith, Kline & French Laboratories Inc., Philadelphia, Pennsylvania); William Weiss (Chief, Office of Biometry, NINDS, Bethesda, Maryland); Dixon M. Woodbury, Ph.D. (Professor of Pharmacology, College of Medicine, University of Utah, Salt Lake City, Utah).

The Committee met for the first time April 11 and 12, 1969. The development of the Institute's epilepsy program leading to the establishment of the Section on Epilepsy was shown. The Section's activities were noted: surveys, symposia, Epilepsy Abstracts, television application, and anticonvulsant drugs. The Committee discussed the problems encountered by the pharmaceutical industry in their development of anticonvulsant drugs, all of which reflect either small market potential or the difficulty in obtaining adequate clinical trials of new anticonvulsant drugs. The Committee reviewed the Section's anticonvulsant drug program and noted anticonvulsant drugs in clinical, preclinical, and shelved status. Institute-sponsored evaluations of promising anticonvulsant drugs were discussed. Finally, the Committee reviewed pharmacological data on 5 drugs submitted to the Institute for consideration. The Committee recommended the following:

1. NINDS should sponsor anticonvulsant drug testing and clinical trials.

2. Research contracts should be used for support of this program.

3. First priority for NINDS anticonvulsant drug studies should be drugs in IND status; as the program grows drugs in earlier status may be supported.

4. With respect to specific anticonvulsants discussed sulthiame should be the subject of an NINDS sponsored trial.

Activities of the Public Health Service Advisory Committee on the Epilepsies, including meetings in November and May, were supported by the staff of this Section. The basic research task force of the PHS Advisory Committee on the Epilepsies recognized that much of the basic research in the neurological sciences during the recent years was of considerable potential value to an understanding of epileptiform seizure mechanisms in man but that this information had not been sufficiently applied for this purpose. It was therefore decided to seek the collaboration of investigators in the field of basic structural and functional neuronal mechanisms, and to hold a symposium and submit the papers for publication in a monograph. The symposium "Basic Mechanisms of the Epilepsies" was held in November, 1968 in Colorado Springs. A monograph consisting of the chapters contributed by the speakers at the symposium and chapters prepared by sumposium discussants will be published in FY 1970 by Little Brown & Co. The head of this Section served as the coordinating member of the editoral board and was responsible for all communications between 66 contributors and publisher, including the compilation of corrected master galley proofs. This endeavor placed added strains on both professional and supporting staff. The symposium was attended by more than 400 scientists and the monograph is eagerly awaited by the scientific community.

Volume 1 (1968) of Epilepsy Abstracts with cumulative index has been enthusiastically received by more than 2500 investigators and clinicians. The computer tape, which contains 8,000,000 characters, for those abstracts published in Volume 1, has been deposited in Data Central for an evaluation of the usefulness of free-text searching. If it is determined to be useful to teachers and investigators, it will be made available through the NINDS information network with additional material being added to the Data Base. In addition to the current publication of Volume 2 of Epilepsy Abstracts, 5800 abstracts from the period 1947-1967 have been sent to the printer and will appear in two volumes.

CONTRACT NARRATIVE
Special Projects Branch--Section on Head Injury
July 1, 1968--June 30, 1969

UNIVERSITY OF MICHIGAN (PH 43-67-1136)
TECHNOLOGY INC. (PH 43-67-1148)
WEST VIRGINIA UNIVERSITY (PH 43-67-1137)

Title: Determination of the Physical Properties of Tissues

Contractor's Project Director: Dr. Verne G. Roberts (Univ. of Michigan)
Dr. Lawrence S. Higgins (Technology Inc.)
Dr. James McElhaney (West Virginia Univ.)

Current Annual Level: $163,035 (University of Michigan)
$241,000 (Technology Incorporated)
$189,000 (West Virginia University)

Objectives: To develop definitive information on the physical properties of the tissues of the head (scalp, skull, dura, brain, fluids); and to develop mathematical solutions for various simple mechanical force problems relating to effect of force upon the head. These objectives represent Phase I and preliminary work on Phase IV of a program to construct and test accurate physical models of the head. Various physical properties such as bulk modulus, shear strength, tensile strength, compressive strength, etc., are being determined using specimens from human cadavers, autopsies, biopsies, and similar specimens from the Macaca mulatta.

Major Findings: The project period represents the second year of this collaborative collected study. Efforts during the first year were generally directed toward developing specialized test equipment and modifications and determining test parameters in terms of loads applied, establishing mechanisms for securing test specimens, and establishing standardized test procedures. During the second year considerable effort has been devoted toward gathering test data through the established test program. Each contractor has proceeded independently with mixed results in comparability of data. Test results to data, however, indicate that sufficient data is on hand to clearly define the properties of cranial fluids (CSF and blood) and the dura. In order to develop definitive information on the more complex tissue structures such as scalp, skull and brain, additional tests will be required. Efforts are under way which will assure comparability of data for common evaluation and analysis and more effective coordination of each contractor's test programs to prevent duplication of test efforts. As a result of these steps, and utilizing data gathered to date, materials testing should be substantially completed by June 1970. In vivo testing has been limited to certain nondestructive tests on the Macaca mulatta limited to brain and skull. Theoretical efforts have yielded mathematical solutions to the problems of torsional loading and direct radio impact on fluid-filled shells.

Significance to NINDS Program and Biomedical Research: It is most important to better understand the effect of various forces of injury upon the brain and skull. Little is known about the anatomical results of various forces and the pathways of destructive forces. Destructive testing in animals and neuropathological studies cannot yield definitive information. The goal of this program is the development of suitable and accurate models to which various stresses and loads can be experimentally applied and the effects accurately monitored. From data derived from such experiments, mathematical models can also be developed. Immediate benefits of ongoing Phase I studies include increased knowledge of the physical properties of the tissues of the head, about which little has been known; and the development and application of certain mechanical engineering test procedures to the mechanical testing of biological materials, a unique contribution to knowledge.

Proposed Course of Contracts: The third year of research is beginning at University of Michigan and West Virginia University. Research at Technology Incorporated is being terminated at the end of the second year. Completion of the studies of the physical properties of tissues is anticipated during the forthcoming or third year. In addition, preliminary work on Phase II, the selection of appropriate nonbiological materials whose properties are similar to tissues, will begin. Phase III, the development and application of forces to physical models; and Phase IV, the development of mathematical simulations, will follow completion of Phases I and II.

CONTRACT NARRATIVE
Special Projects Branch--Section on Head Injury
July 1, 1968--June 30, 1969

NATIONAL ACADEMY OF SCIENCES (PH 43-64-44, Task Order 11)

Title: A 15-Year Follow-Up of Head-Injured Veterans of the Korean Campaign

Contractor's Project Director: Seymour Jablon, M.S.

Current Annual Level: $40,600

Objectives: 1. To provide NINDS with the current addresses of the head-injured veterans participating in the study. 2. To select and locate matched controls. 3. To code the Red Cross interview schedules. 4. To key punch the Red Cross coded forms. 5. To key punch the original coded acute data for the so-called Meirowsky cases. 6. To obtain General Classification Test scores from retired records in St. Louis. 7. To prepare a data tape embodying original (acute) and Red Cross interview information. 8. To prepare tabulations and analyses from the total material, relating work status and the history of posttraumatic symptoms and epilepsy to characteristics of the original wound and its treatment.

Major findings: The contractor has accomplished objectives 1 through 7 and has begun work on objective number 8. Data analysis will be completed by October 1969.

Proposed course of contract: This project will be concluded in fiscal year 1970.

CONTRACT NARRATIVE
Special Projects Branch--Section on Epilepsy
July 1, 1968--June 30, 1969

NEW CASTLE STATE HOSPITAL (PH-43-68-1310)

Title: Study of the anticonvulsant properties of albutoin

Contractor's Project Director: Joseph T. Brock, M.D.

Current Annual Level: $90,000

Objectives: To study the relative anticonvulsant properties of albutoin administered to refractory patients alone and concurrent with other anticonvulsant drugs; and to evaluate the possible side effects of albutoin.

Course of Contract: The major portion of the year was required to prepare for the clinical studies. The following were achieved: selection of patients eligible to participate in study from population of 800 patients; informed consent obtained for more than 100 patients; grouping of patients into latin square design by NINDS experimental design consultant; physical relocation of the group patients into special wards; preparation of medication in double blind manner, involving cooperation of three pharmaceutical companies and preparation and packaging into 1 week units of 114,000 capsules; purchase and delivery to the hospital of automated clinical laboratory equipment; refinement of blood level determination techniques by chemist, New Castle State Hospital; and, pilot study of two patients to prove albutoin blood level method.

The above accomplishments reflect the considerable effort required to "tool up" for drug evaluations. It is anticipated that actual patient trials will begin June 15, 1969.

Major Findings: The project period was required for preparation as noted above. Major findings will accrue in the coming fiscal year.

Significance to NINDS Program and Biomedical Research: Although new, improved anticonvulsant agents are necessary, the pharmaceutical industry has demonstrated little interest in this area. One of the industry's major problems is to obtain satisfactory clinical studies of anticonvulsants. It is this problem to which NINDS has addressed itself, and the subject contract is the first NINDS support clinical study of anticonvulsant drugs. It is anticipated that well controlled studies of this type will be very significant indicators of the therapeutic merit of new anticonvulsant drugs and thus encourage industry to develop and submit promising new agents for clinical trial. Drugs exhibiting superiority to presently available anticonvulsants would be further pursued by the company with the aim of eventual marketing and general availability of the drug.

Proposed Course of Contract: The contract will be amended to extend the performance period into FY 1970, to allow for the substantial preparation

time required. Following the albutoin study, other promising anticonvulsants are expected to be evaluated in turn.

Serial No. NDS (CF) - 67 SP 1324
1. Collaborative & Field Research
2. Special Projects Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Collaborative Study of Epilepsy, Phase I

Collaborating Investigators: Fritz E. Dreifuss
J. Kiffin Penry
J. Preston Robb
C. Wesley Watson
Philip T. White

Other Investigators: Pearl D. Fisher
William Weiss
David J. Goode

Cooperating Units: Division of Neurology, University of Virginia Medical School; Montreal Children's Hospital; Division of Neurology, New England Medical Center; Division of Neurology, Marquette University Medical School.

Man Years:

Total:	6-8/12
Professional:	2-4/12
Other:	4-4/12

Project Description:

Phase I of the Collaborative Study of Epilepsy is a pilot project which was initiated July 1, 1966. The main end towards which a study of the problem of epilepsy is directed includes: (1) The identification and evaluation of conditions associated with or developing from the illness. (2) The extent to which the course of the illness could be altered and an evaluation of methods accomplishing this. (3) Investigation of possible etiological factors simply and in association with each other.

The need for a large cohort of patients selected on the basis of rigid standards for whom the manifestation of the disease are currently and reliably recorded is stressed. A collaborative effort was undertaken by four clinical centers, namely: Boston, Charlottesville, Milwaukee, and Montreal. These centers gave the greatest hope of providing an adequate case load for a collaborative study. The coordinating center was established within the Section on Epilepsy, C&FR, NINDS, for Phase I. It was stressed that the objectives of the proposed pilot study differ, in the large, from the long range study of epilepsy. The primary purpose of the full scale study is to find answers for unsolved problems on epilepsy. The pilot phase is designed

to provide and to test means for developing this information. The general aims are to demonstrate that diverse clinical centers can work together in a uniform manner as regards clinical procedures and laboratory examinations, to further develop and thoroughly test a protocol jointly prepared by the clinical directors with the assistance of study design consultants, and to develop a mode of data storage, retrieval, and analysis, utilizing biostatistical guidance and computer techniques.

The specific aims of the pilot study (Phase I) are: (1) To test protocols for practicality and for completeness in providing required medical data. (2) To measure consistency among collaborating institutions in the selection of patients, using specified testing procedures. (3) To measure the reliability of observations, using specified testing procedures. (4) To test the operation of the coordinating center: (a) To determine whether or not the protocol had been followed, and (b) to observe what the record said and to see if this is what the investigators meant. (5) To test the quality control aspects of the uniformity and the processing of study data, i.e., the administration of the data processing and the accuracy with which data are coded, transcribed and stored in the computer. (6) To provide sufficient material to demonstrate procedures for the summarization and statistical evaluation of the project data, so as to enable clinicians to appraise results of the eventual program with a minimum of delay. (7) To develop and test computer programs for the production of summarized information, statistical analysis, and information on quality control.

To achieve these objectives, a segment of the problem of epilepsies, the recurring absence attacks, are studied in selected detail. This type of seizure disorder was chosen because (1) much remains to be learned concerning its etiology, the site of origin within the brain, its relationship to central nervous system maturation, and its therapy. (2) It can be precipitated and observed by simple office procedures (hyperventilation). (3) It occurs with sufficient frequency to permit the accumulation of considerable data. (4) Reasonably objective measurements of its occurrence and its manifestations are available. (5) The withdrawal or modification of medical regimens is less likely to be associated with serious complications than would be true of other seizure forms. As indicated above, the purpose of the pilot study is not primarily to develop medical information, but rather to provide and test the means for developing such information.

Achievements: The last patient was admitted to study on April 30, 1968, resulting in a total of 172 patients. With the exception of those lost to study, all patients were examined as planned in follow-up visits (initial, 1st month, 4th month, 10th month, 16th month, and 22nd month) through December 31, 1968, when acquisition of clinical data ended. The number of patients completing the follow-up examinations was as follows: 1st month--171; 4th month--167; 10th month--152; 16th month--109; 22nd month--54. Only nine patients were lost to follow-up visits throughout the entire study, and this ratio of 5.2% was less than anticipated.

A coding manual for all data was completed and distributed to all investigators for use in retrieval and interpretation of data. All data was placed in the master magnetic tape file. The initial requests for retrieval from all investigators were accomplished; secondary requests are being programmed. One manuscript, "Psychometric Findings in Petit Mal Epilepsy (Absence)" was completed by the group and is ready for submission to the publisher; two others are in final draft. Reliable data on 75 patients followed over 16 months on Zarontin was supplied to Parke-Davis & Company to support their New Drug Application for Liquid Zarontin.

Major Findings to date are: (1) Detailed clinical data on epilepsy can be collected, coded for automatic retrieval, and subsequently pooled with a known and satisfactory degree of reliability. (2) Accuracy of data collection and reliability of description can be significantly improved by use of video-recording techniques, such as instant replay or storage of clinical data in video-tape form. (3) The classification recommended by the Committee on Classification of the International League Against Epilepsy for the absence attack under the subcategory "generalized non-convulsive seizures" was found to be inadequate for describing and categorizing a single seizure explicitly. (4) An unpredicted trend in skeletal age retardation was found among the patients entered into the study which warrants further investigation into skeletal development rates of epileptics. (5) The study patients were largely normal neurologically with speech defects cited as the most common neurologic abnormality. (6) Psychometric evaluation revealed a significantly high proportion of the study population to be mentally defective or of borderline intelligence. Mental retardation could be related to neurologic abnormalities, occurrence of motor manifestations during the absence attack, early age of onset of absence, and socio-economic factors. On retesting of 93 subjects, no deleterious effects of ethosuximide on psychometric performance were found.

Proposed Course: By December 31, 1969, 6 manuscripts describing the major findings of the study will have been submitted for publication. A final comprehensive report will be completed. Video-recording techniques and data collection techniques developed in the pilot phase will be utilized in FY 70 in two clinical drug studies.

Honors and Awards:
None

Publications:
None

Serial No. NDS (CF)- 69 SP 1784
1. Collaborative and Field Research
2. Special Projects Branch
3. Bethesda, Maryland

PHS--NIH
Individual Project Report
December 1, 1968 -- June 30, 1969

Project Title: A Survey of Current Head Injury Research

Previous Serial Number: None

Principal Investigator: R. Wayne Hurt, M.D.

Other Investigators: J. Kiffin Penry, M.D.
Claire Kretschmann

Man Years:

Total:	1.3
Professional:	0.7
Other:	0.6

Project Description:

Objective: A comprehensive and in-depth analysis of current research in head injury is the chief objective of this effort. An attempt is being made to identify investigators conducting current programs in head injury research and to determine the institutions involved, specific areas of investigation, and the source, amount, and type of funding. Another objective is detection of overlapping areas of research where unnecessary duplications in effort may be involved and discernment of neglected areas where greater research emphasis should be applied to prevent a bottleneck to progress.

Methods Employed:

1. Scope of search established by defining a current head injury project to be a project active on or after January 1, 1969, which is devoted partially or exclusively to a study of mechanical trauma to the skull and/or its contents. Projects included are concerned with one or more aspects of the head injury problem such as basic mechanisms, sequelae, diagnosis, treatment, prevention, epidemiology, socio-economic features, or medico-legal considerations.

2. Ascertainment of investigators with current research programs in head injury is being accomplished by consulting the following information sources:

a. Resumes from grant, contract, and direct operation registries such

as those provided by the Science Information Exchange and the Defense Documentation Center.

b. Special reports and surveys such as the Research Grants Index, Neurological Research: Summaries and Index of Current Research, and Survey of Research Facilities and Manpower in Brain Sciences in the United States.

c. Literature and bibliography searches such as the Medical Literature Analysis and Retrieval System (MEDLARS) of the National Library of Medicine and Current Contents: Life Sciences.

d. Consultation with administrative officers and scientists in various governmental and nongovernmental organizations such as the Environmental Control Administration, Veterans Administration, National Highway Safety Bureau, National Academy of Sciences--National Research Council, National Safety Council, and American Society of Trauma.

e. Consultation with officials, scientists, and clinicians in foundations, industrial organizations, and universities.

3. Whenever possible, the information sought for each current project includes names and disciplines of principal and coinvestigators; name and location of performing institution; source, amount, and type of funding; actual and planned duration of project; and specific area(s) of investigation involved. As it is obtained, this information is coded and stored on magnetic tape.

Major Findings: Although this survey will not be completed for several weeks, there are approximately eighty current projects in the United States concerned with the problem of head injury as defined. About two-fifths of these are supported by the National Institute of Neurological Diseases and Stroke and another one-fifth by other administrative units within the Department of Health, Education, and Welfare. A detailed presentation of the findings in this survey will be the subject of a report in July 1969.

Significance to biomedical research and the program of the institute: A comprehensive analysis of current research programs in head injury should provide useful guidelines for reducing duplication in efforts and directing attention to those areas where additional support may be required.

Proposed Course: The present survey will be completed by mid 1969. However, the methods used could easily be adapted to serve as a means of continued surveillance and analysis of programs concerned with the problem of head injury.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 SP 1785
1. Collaborative and Field Research
2. Special Projects Branch
3. Bethesda, Maryland

PHS--NIH
Individual Project Report
July 1, 1968--June 30, 1969

Project Title: A 15-Year Follow-Up of Head-Injured Veterans of the Korean Campaign

Previous Serial Number: None

Principal Investigators: A. R. Taylor, M.B., FRCS
S. Jablon, M.S.

Other Investigators: W. F. Caveness, M.D.
A. M. Meirowsky, M.D.
A. C. Dresser, M.S.W.
R. W. Hurt, M.D.
C. Kretschmann

Cooperating Units: National Research Council Follow-Up Agency, Washington, D.C.
American National Red Cross Service to Military Families, Washington, D.C.

Man Years:

Total:	2.0
Professional:	1.0
Other:	1.0

Project Description:

Objectives:

1. To obtain information on employment patterns and the incidence of posttraumatic symptoms and epilepsy over the past 15 years in a group of head-injured veterans of the Korean Campaign.

2. To relate these findings to the initial data on the severity, therapy, and sequelae of the injuries; and to compare the status of the injured men to that of a group of non-injured control subjects.

3. By determining the incidence of seizures in the parents, siblings and children of the veterans, to see if a genetic factor might be involved in predetermining epilepsy after head trauma.

4. To identify those veterans who would be willing to participate in a comprehensive 15-year follow-up hospital evaluation.

Methods employed: Acute data were supplied by Dr. Caveness and Dr. Meirowsky. The National Research Council Follow-Up Agency took a 30 percent sample of the injured group and selected non-injured controls who were in Korea in the same units as the injured men at the time the head injuries were sustained. Current addresses, induction AGCT scores and pre-induction employment of the injured and non-injured men were obtained by the National Research Council Follow-Up Agency. The staff of the Section on Head Injury obtained permission of the veterans for interviews. American National Red Cross Service to Military Families workers interviewed the veterans, member of their families, and their employers. The medical data were edited by the staff of the Section on Head Injury. The National Research Council Follow-Up Agency edited the employment information, coded the interview schedules, and transferred all acute and follow-up data to a seven-track tape file.

Major Findings: Data analysis will not be completed until October 1969.

Significance to biomedical research and the program of the institute: This study will provide data on employment and the posttraumatic state fifteen years following head injury.

Proposed course: Upon completion of the data analysis, Dr. Taylor and Mr. Jablon will submit their report to the Director of the National Institute of Neurological Diseases and Stroke; original case data will be returned to Drs. Caveness and Meirowsky, and the interview schedules will be returned to the Red Cross Service to Military Families.

Honors and Awards: None

Publications: Dresser, Astha C.: Work status following head injury. In Walker, A. E., Caveness, W. F. and Critchley, M. (Eds.): Late Effects of Head Injury. Springfield, Ill., Charles C. Thomas, in press.

Serial No. NDS (CF) - 69 SP 1786
1. Collaborative & Field Research
2. Epilepsy Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Automatisms associated with the absence of petit mal epilepsy.

Principal Investigator: J. Kiffin Penry, M. D.

Other Investigators: Fritz E. Dreifuss, M. D.

Cooperating Units: Department of Neurology, University of Virginia School of Medicine, Charlottesville, Virginia.

Man Years:

Total:	1/12
Professional:	1/20
Other:	1/30

Facilities and Equipment:

EEG Laboratory of the University of Virginia Medical Center. Complete video tape recording equipment dual camera input; (two EEG-FM transmitters, two FM receivers). Two channel EEG telemetry system, supplied by the Epilepsy Section.

Project Description:

The association of ictal automatisms with epileptic lesions of the temporal lobe and Penfield's production of automatisms by stimulation of gray matter near the insula have resulted in the general belief that automatisms are caused by discharge of an epileptic focus within the brain. Occurrence of automatisms in association with petit mal epilepsy, where there is no apparent single focal lesion, though well documented, has not been adequately explained. Systems for classification of automatisms have been proposed by Lennox, Penfield and Jasper, and Gastaut.

The purpose of this study was to determine the influence of pre-ictal and ictal stimuli upon the occurrence and character of automatisms of the absence attack of petit mal epilepsy.

Methods Employed: Patients who suffer from recurring absence attacks associated with generalized spike-wave discharge in the EEG were selected

by Dr. Dreifuss and scheduled for study in the EEG laboratory of the University of Virginia Medical Center where the Section on Epilepsy maintains video-tape recording equipment, including multi-camera input, and EEG-FM transmission and reception equipment. Two channels of EEG from 4 leads are FM-telemetered to a conventional EEG apparatus. The resulting EEG tracing as well as a full view of the patient are video-recorded by means of a split-screen technique. A series of pre-ictal stimuli, consisting of motor activity in terms of walking in place, finger-tapping, hand-clasping, rubbing or scratching, and chewing gum, were delivered prior to the precipitation of a seizure by hyperventilation. Pre-ictal commands to clasp hands after the onset of an absence attack were given to each patient. Stimuli delivered during the absence attacks, either spontaneous or induced, were: Tickling the skin with cotton wool, light pin prick, and verbal command. Video-tapes of the patient's activity and his simultaneous EEG record were extensively replayed for thorough analysis of the absence attacks and characteristics of the patient's responses. A total of 12 patients were studied.

Major Findings: A study of 93 absence attacks in 12 patients revealed automatisms to be a common accompaniement of absence attacks in petit mal epilepsy. Only ictal automatisms were observed. Both perseverative and de novo automatisms were easily induced and influenced by environmental stimuli. All automatisms occurred in relation to generalized 3/sec. spike-wave discharge recorded from scalp electrodes. There was no evidence of focal discharge from temporal lobe at any time. These findings emphasize a need for further study of behavior during generalized spike-wave discharge and point out the lack of specificity of automatisms for clinical diagnostic purposes.

Significance of Biomedical Research to the Program of the Institute: This study has contributed to the epilepsy program of the Collaborative & Field Research Division, and it has applied video-recording techniques to improve the quality of clinical research.

Honors and Awards:

None

Publications:

Penry, J. K. and Dreifuss, F. E.: Automatisms Associated with the Absence of Petit Mal Epilepsy. Arch. Neurol. (in press) 1969.

Serial No. NDS (CF) - 69 SP 1787
1. Collaborative & Field Research
2. Epilepsy Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Detection of clinical manifestations of brief spike-wave activity.

Principal Investigator: David J. Goode, M. D.

Other Investigators: J. Kiffin Penry, M. D.
Fritz E. Dreifuss, M. D.

Cooperating Units: Department of Neurology, University of Virginia School of Medicine, Charlottesville, Virginia.

Man Years:

Total:	3/40
Professional:	1/20
Other:	1/40

Facilities and Equipment:

Electroencephalographic equipment and space for testing will be provided by the University of Virginia Hospital at Charlottesville. Pursuit Rotor, button-pressing apparatus, video-recording apparatus, and telemetry equipment will be provided by the Section on Epilepsy.

Project Description:

Objectives: The purpose of this study is to determine whether brief episodes of spike-wave activity will interfere with performance of a complex, continuous test such as the pursuit rotor which requires continuous visual and proprioceptive feedback. Continuous rapid button pressing will also be tested to investigate any changes of rate or rhythm produced by spike-wave. The time relation of motor impairment to electrical discharge will be apparent from simultaneous recordings of performance and EEG.

Methods employed: One of the first investigations of psychological parameters during spike-wave activity was Schwab's studies of reaction time in petit mal. (1, 2) Patient's response (squeezing of a rubber bulb) to auditory and visual stimuli was found to be delayed during spike-wave activity. In 1953 Schimazono, et al, (3) investigated consciousness during spike-wave. Response to verbal stimuli and repetitive string-pulling was measured. They described the petit mal attack as a disturbance in consciousness grading from almost no change to total loss and involving a trough-like

course, during which consciousness is less impaired early and late in the seizure. More sophisticated techniques have been employed by Tizard and Margerison (4), and Mirsky and Van Buren (5). Tizard measured the effects of spike-wave discharge on performance of simple auditory, visual, and tactile reaction tests as well as more complex discrimination tests. They conclude that brief discharges, with no apparent clinical accompaniment, may be detected by alterations in response time and increased errors. Much individual variation as well as a variety of impairment was found, depending on the degree to which the capacity of the brain to process information is affected. Mirsky and Van Buren used a "continuous performance test" requiring a discriminatory response to a series of visual signals. They noted that during this test correct responses were obtained 25% of the time during spike-wave episodes.

The patients will be supplied by Dr. Dreifuss and the tests will be administered by Dr. Goode. Patients must be between 9 and 18 years of age.

Each patient will be trained for about one hour on the tests prior to recording. Then electrodes and 2 EEG-FM transmitters will be connected to the patients. 2 channels of EEG and one channel of output from the test apparatus will be monitored on the Grass Polygraph. A full view of the patient will be video-recorded on one-half of a split screen. On the other half of the screen, a detailed view of the pursuit rotor and the 3 channels of the polygraph will be recorded. Later observations of the television and the written record will enable time correlations of lapses in performance with the EEG abnormality.

Major Findings: To date, 11 patients have been tested according to the outlined protocol. 6 patients were found to have spike-wave activity during the test period, and a total of 100 bursts of spike-wave have been analyzed as to their effect on pursuit-rotor performance. For brief spike-wave discharge (<2 sec.) no consistent impairment of pursuit-rotor performance has been found. In fact, in several cases, excellent performance has been maintained during prolonged spike-wave activity.

Significance to Biomedical Research and to the Program of the Institute: It is felt that a true measure of continuous performance has not been made. Mirsky and Van Buren's tests as well as those of Tizard have consisted of discrete stimuli requiring discrete responses. Continuous motor performance tests involved repetitive simple tasks which are likely to be continued as perseverative movements during spike-wave discharge. The pursuit-rotor requires continuous visual attention with complex coordination. It is believed that brief lapses of attention will be detected more readily by this test and the time course of the disturbance of consciousness will be more adequately measured.

Proposed course: Because of a large individual variation of the effects of spike-wave found in the course of study, it is proposed to continue testing until 2 additional patients who have brief bursts of spike-wave activity have been recorded.

HOW TO USE
THESE SEPARATORS

Use one page for each separation.

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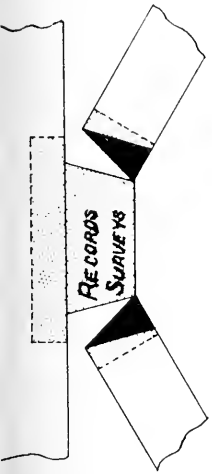

TABBED SEPARATOR SHEET
Form HEW-69
(3-56)

ANNUAL REPORT
For Period July 1, 1968 through June 30, 1969
Perinatal Research Branch
National Institute of Neurological
Diseases and Stroke
National Institutes of Health

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ANNUAL REPORT
For Period July 1, 1968 through June 30, 1969
Perinatal Research Branch
National Institute of Neurological
Diseases and Stroke
National Institutes of Health

SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACCOMPLISHMENTS

During the past year, the major activity of the Perinatal Research Branch has continued to be concerned with the direction, coordination and execution of the Perinatal Research Project. This program which started in 1959, terminated the obstetrical intake on December 31, 1965, and has completed the examinations of all children through age one.

About 30 percent of the children have been examined at age seven, and are completing their examination schedule.

This project was reviewed in detail by the Ad Hoc Statistical Committee, under the Chairmanship of Dr. Abraham M. Lilienfeld, and the report and recommendations of this group became available in December, 1968. All but two of the recommendations of this Committee have been implemented. The recommendation to discontinue the 8-year speech and hearing examination has been subjected to additional review by the evaluation of the quality of the data collected at eight years. Because of the high quality of these data the examination is continued and another evaluation of the data is scheduled a year from now.

The recommendation to reduce the workload through sampling of children beyond age four for examination at seven and eight years of age is still undergoing careful evaluation.

The project is being directed by the Chief of the Perinatal Research Branch, operating with the advice of the Perinatal Research Committee. This Committee was recently expanded through the addition of Dr. Schuyler Kohl as Chairman, and Dr. Abraham M. Lilienfeld.

Data collection in the Perinatal Collaborative Project at age four, seven and eight years has continued in 12 participating collaborating hospitals. Concurrent evaluations indicate that about 77 percent of the eligible children have actually been examined at age seven. Of the remaining portion of children, addresses are known on about half of them, and half of them have been lost to study. Efforts have been under way for sometime to make arrangements with the Social Security Administration and the Internal Revenue Service to aid in the tracing of children and in the contacting of their parents to elicit their continued cooperation in this program. In view of the current manpower shortage, it will be necessary to complete the assessment of children lost to study for evaluation of bias through contractual arrangements with outside investigators.

Continuous evaluation of the quality of the collected information is a major activity. Re-examination of a portion of children by examiners from other institutions is done at intervals of three months, involving all institutions and covering the 4-year, 7- and 8-year examinations. Results of these continuous examinations show acceptable standards of quality and reliability in keeping with the published results of other investigations. The cost of this project continues to remain relatively high. The actual expenditures do not show the expected decrease because of a decreased workload. This is largely due to the increase in cost in running this program because of substantial salary increases of personnel in the participating hospitals, and in some instances increases in the overhead costs of our contracts. According to our calculations during FY 1968, nine percent of the contract expenditures were due to increases in salaries and in overhead costs, as compared to Fiscal 1967. We are experiencing similar cost increases in FY 1969.

Responding to increasing demands for prudent expenditures in research, we are considering a number of options to reduce the workload and the cost of this project, but also affect the potential of the program in reaching its primary objectives in various ways. These options are being subjected to detailed analysis at this time.

Another major activity of the Perinatal Research Branch in cooperation with the Office of Biometry lies in the area of data evaluation and data analysis. Considerable progress has been made to produce summary tapes, particularly the so-called variable file, incorporating the most important variables collected on the Collaborative Project population. This has reduced the master file considerably in an effort to reduce the cost and the turn-around time. Data analysis has continued,addressed to specific questions posed by investigators from the Perinatal Research Branch and from the Collaborating Institutions which have produced many preliminary findings which are detailed in the reports from the various sections. The data analysis effort has been broad in scope and detailed. Limiting factors of this effort are in part due to the small number of systems analysts available to this program resulting in delays in the preparation of specifications for the analyses, and the lack of contact between investigators and programmers.

The great demand for systems support and programming has however largely come about because of the interest to serve the many needs of the project participants in data analysis, resulting in the development of tailor-made jobs in response to specific requests. While this has served a purpose, and has provided for the participation of large numbers of people in the analysis of the data, it has served as a deterrant from the systematic analysis of the main body of data in line with the major objectives of the Study, namely the identification of pre- and perinatal variables related to neurological and mental deficits of childhood. It is for this reason that a data analysis plan has been developed, detailing specific areas for major effort and establishing priorities designed to develop promptly and efficiently the information on the identification of pre- and perinatal variables related to

neurological and mental deficits of childhood as they can be identified in the data already collected on the Collaborative Project population. This plan is being implemented at the present time.

In addition, a detailed outline has been prepared and is in the data processing phase to produce a comprehensive set of basic data on the Collaborative Project population. This will include the characterization of the Study sample by demographic variables, medical and obstetrical characteristics, past pregnancy history, labor characteristics, neonatal characteristics, and the major child characteristics through age four. This output includes an evaluation of the bias introduced through losses, missing information, the evaluation of the comparability and uniformity of data collection in various institutions, and the assessment of the poolability of our data.

To give outside program participants an opportunity to participate in these endeavors, these data are developed in such a manner as to provide them with the frequency of basic variables as well as relationships of these variables to specific neurological and mental deficits for their Study population. Also, program participants have been invited to identify interests in the analysis of major blocks of data that are part of the primary objectives of this program.

Finally, PRB has established this year a mechanism for the systematic and objective merit review of all study proposals submitted by Project professionals for the analysis of Core data. The Data Analysis Board, since its inception in August 1968, has held 28 regular, almost weekly, meetings and reviewed not less than 150 requests. The decisions of the Board are accurately recorded and communicated to the authors. This procedure has exercised a standardizing and coordinating influence on the research productivity in the Project, both as to merit, effort and cost.

PROGRAM ACCOMPLISHMENT

The continued analysis of data on the problem of clinical indicators of asphyxia-anoxia has further supported the notion derived from preliminary analysis that these do not appear to be of major importance in severe neurological and mental deficits. The emphasis has to be on severe, in view of the fact that these analyses were based on neurological endpoints derived from the examination of 1-year old children, which while identifying most of the serious neurological deficits, do not adequately define nor identify children with soft neurological signs.

Further analysis supports preliminary findings of a strong association of diabetes in pregnancy to intellectual performance in 4-year old children. Offspring of diabetic mothers, particularly when diabetes is complicated by acidosis or acetonuria, show considerable lowering of I.Q. at four years, as compared to matched controls. Also, further analysis has provided additional support that acetonuria without diabetes in pregnancy is associated with depressed intelligence in 4-year old children. Many other indirect parameters of maternal nutrition have been explored, including anemia of pregnancy, twinning, and rapid succession of pregnancy as factors in intellectual functioning of 4-year old children.

Rapid succession of pregnancy has some effect on the development of the offspring. Children born with short inter-sibling intervals have significantly lower birthweights, lower mental and motor scores during the first year of life, and lower I.Q.'s at four years. Also there was some increase in neurological abnormalities among this group of children.

A very important development was the identification of the measles virus in biopsy material from patients with subacute sclerosing panencephalitis. This was the result of the application of a new tissue culture technique. This technique is now being applied to biopsy specimens of patients with multiple sclerosis and other neurological diseases for which there is indirect suggestive evidence that they might be virus induced.

Further evidence has accumulated that rubella infections during the second trimester affect the fetus. A number of instances have now been identified in which congenital infection of the child, when the mother was infected with German measles in the second trimester, has been proven through serological determinations and virus isolation from the youngster. Also certain defects including growth retardation and hearing loss have been observed in some children.

The analysis of relationships of developmental measures assessed in 8-month old children to intellectual performance at four years has turned up rather interesting correlations. These point out that early developmental measures have some predictive albeit limited value for later performance. A most interesting observation here was the difference in prediction by social characteristics as follows. Whereas poor mental and motor development during the first year of life of children of average or above average social background was not related to intellectual performance at four years, poor performance at 8 months of children of poor socioeconomic background was strongly related to poor performance at four years. From this data it seems possible to differentiate among children of low social class at 8 months poor performers who are likely to be poor performers at 4 years and good performers who are likely to be good performers at 4 years. This finding is of considerable significance in view of the many efforts that have been made in recent years to identify poor performance early in life, particularly among low socioeconomic groups where environmental deprivation may play an important role, in an effort to provide such groups with enriched environmental experiences in preparation for schooling. While our data do not permit us to speculate about the likelihood with which such programs might be successful, they nevertheless clearly indicate an ability to identify early in life, at eight months, children from low socioeconomic backgrounds who will perform poorly at 4 years.

PROBLEMS

The most serious problem is the current restriction in recruitment in the face of a continuing attrition of personnel. Such restrictions in recruitment are bound to affect complex programs as are conducted by the Perinatal Research Branch much more substantially than the more typical intramural operation of an individual investigator with a small team working on a rather circumscribed specific problem. The workload of this project was

predetermined when the decision for its inception was made years ago. Inadequate, or in part, total lack of appreciation of need for staffing of such a program in central direction resulted in a considerable backlog of information collected by this program for a number of years before sufficient staff could be recruited to handle the workload. While backlogs in review, coding, and evaluation of data have been removed, continuous monitoring, in terms of quality control, and substantial preparation for data analysis has only recently become possible. We are faced now with the loss of five professional staff members by the end of this fiscal year who have been instrumental in carrying forth the quality control program. There are as of now no positions available to replace them. In addition, it has been repeatedly recognized that the Branch needs to be strengthened through the recruitment of competent epidemiologists to expedite the current data analysis effort. Also, we need to obtain a position to recruit the Head of the Data Management and Retrieval Section of PRB. Attempts to recruit the Assistant Head of the Branch have not been successful for several reasons. These are the scarcity of senior epidemiologists with administrative experience who would be interested to serve in this rather complex project, the low financial reward in comparison to similar positions in universities, the continuing relatively poor image of this project among influential members of the scientific community at large, and the very cumbersome decision-making process which is part of this Collaborative Project.

ACKNOWLEDGMENT

I would like to acknowledge the considerable support which this program has received in data processing and data analysis by the Office of Biometry of the NINDS. Specifically, I like to acknowledge the contributions made by Mr. Sciabbarrasi, from the Office of Biometry, and the group of systems analysts which he directed on assignment from the Office of Biometry to the Perinatal Research Branch.

PUBLICATIONS AND PAPERS PRESENTED

Berendes, Heinz W. and Churchill, John A.: Prenatal Causes of Mental Retardation - A Report of Work in Progress. Presented at XII International Congress on Pediatrics in Mexico City, December, 1968.

Berendes, Heinz W.: Cerebrale Spatschaden nach perinataler Asphyxie. Der Gynakologe, 1, 1968, Pp. 94-98.

Niswander, K. R., and Berendes, H.: The Effect of Maternal Cardiac Disease on the Infant. Clinical Obstetrics and Gynecology, Vol. 11, No. 4, December 1968.

A. SECTION ON OBSTETRICS

Report for the Period July 1, 1968 through June 30, 1969

I. SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACCOMPLISHMENTS

The staff of the Section has been fully engaged (85 per cent of man years) with the completion and updating of the obstetric data file. The gravidity and parity of the Study gravidae have been reviewed. The data on all twin pregnancies and all fetal deaths have been completed. An analysis of the reporting of toxemia by Study hospital over the course of time of the Study has been initiated.

The completion of the obstetric data file has been considered a prerequisite before a systematic analysis of the Collaborative data can be undertaken. It was therefore decided to devote practically all available manpower to accomplish this goal. Plans for the analysis of the obstetric data have been developed.

II. PROBLEMS

The freeze on positions has made it impossible to fill staff vacancies, even though specially competent candidates were available. The Section requires the appointment of at least one additional research-oriented obstetrician.

III. PROPOSED FUTURE OBJECTIVES

1. Description of the major obstetric characteristics of the Study gravidae. Age and gravidity/parity of the Study gravidae, prior obstetric history, medical and obstetric complications of the Study pregnancy, labor and delivery, outcome of pregnancy, duration of pregnancy and birthweight are those variables that can best be described by a series of frequency tabulations. Such tabulations will be produced as soon as possible.

2. A study on the epidemiologic and medical factors in toxemia is presently designed to evaluate the different pathologic and diagnostic variables that are agglomerated in the present definition of toxemia of pregnancy.

I. SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACCOMPLISHMENTS:

The Pediatric Neurology Section has been involved in intensive activity of data analysis.

The first undertaking was to design studies to test hypothesis previously worked out elsewhere. The objective was to test the utility of PRB data. The objective was attained and reported to the Lilienfeld Committee.

The second phase was to run specific studies testing new hypotheses; and in doing so to learn of limitations, procedures and other problems inherent in handling the data.

The third phase, occupying much of the past year, has been to hammer-out a methodology having general application for in-depth analysis of data in such a way that studies of particular factors can be conducted systematically, rapidly, and coherently.

The procedure taken together with definition of a basic cohort of cases (a constant denominator of cases), condensation of complex sources of items into a simplified variable file, and data reduction should now be workable.

Itwould be most helpful to have some sort of rapid computerized way to array data in new combinations. At present, we are faced with either time delay or hand tabulations to this purpose.

Synopsis of Projects:

A. Perinatal Research Branch Data:

The main research effort has been directed along three lines:

Group 1) Study of maternal factors which may impair intrauterine development leading to indicators of defective cerebral formation and maturation in the offspring.

Group 2) Study of mechanical factors of labor which may damage the infant's brain.

Group 3) Study of spastic diplegia of prematurity.

Group 1 Studies:

a. Maternal diabetes:

Churchill, John A., Berendes, Heinz W., and Nemore, J. paper entitled, "Neuropsychological Deficits in Children of

Diabetic Mother" accepted for publication by American Journal of Obstetrics and Gynecology. Further work is planned, and in this we would like to include and have assistance of Dr. James Drorbaugh, Boston, and additional diabetic mothers.

b. Acetonuria:

Churchill, John A., Berendes, Heinz W., and Willerman, Lee. paper entitled, "Gestational Acetonuria and some Developmental Measures in the offspring" presented at American Association of Public Health, November 10-14, 1968, Detroit, Michigan.

c. Proteinuria without Hypertension:

Rosenbaum, Arthur L., Churchill, John A., Shakhashiri, Zekin A., and Moody, Richard, L. paper entitled, "Neuropsychologic outcome of children whose mothers had proteinuria during pregnancy" published in Obstetrics and Gynecology, January 1969.

d. Rapid Succession of Pregnancy:

Rosenbaum, Arthur L., Holley, Wilbur L., and Churchill, John A. paper entitled, "The effect of rapid succession of pregnancy on the neuropsychological development of the offspring" presented at meeting of Society for Research in Child Development, March 26-29, 1969, Santa Monica, California.

e. Hypertension with and without Albuminuria:

Holley, Wilbur L. and Churchill, John A. Preliminary study revealed that mothers with albuminuria and hypertension (whether diagnosed toxemia or HCVD) had small-for-dates offspring with lower IQ than matched controls. Controls were not concurrent and more subjects had become available. Thus, a more encompassing and better controlled study was designed. Severe troubles were encountered in several phases in the data extraction procedure. We still cannot explain important apparent discrepencies.

Analysis of data as it stand shows no significant distinction in outcome of hypertensive-albuminuric subject group and controls. Results are unsatisfactorily ambiguous.

We think the problem must be attacked from a different point of view which we can do.

f. Antibiotics during Pregnancy:

Hypothesis: Gravida receiving antibiotics in last trimester of pregnancy have offspring that test higher in IQ than non-treated controls, perhaps because altering bacterial flora permits better amino acid absorption.

1. Tetracycline: Results of study support the hypothesis.

2. Chloromycetin: No significant difference found.

3. Penicillin: No significant difference found.

The studies have been completed but not reported because of uncertainties. The number of tetracycline cases was rather small. The results of other antibiotics are not supportive. Penicillin may differ because cases used were those on the drug over many months' time, mothers being treated for rheumatic fever. In this time, bacterial flora may have become stabilized.

Allowing time for more tetracycline cases to accrue, a further analysis of data will be done, using the improved matching procedure.

g. Failure of maternal weight gain: a comparison of outcomes of infants whose mothers failed to gain more than ten pounds during pregnancy to those gaining 25 to 35 pounds. Churchill, John A. and Holley, Wilbur L.

From data printed out, we have not been able to demonstrate an association between maternal weight gain and Bayley developmental scores or 4-year IQ. An apparent difference in birth weight disappeared when weight gain was made proportional to maternal weight, and where short gestations were removed from the study.

One would think a' priori' that maternal weight gain ought to be coupled with nutritional impairment, thus influencing outcome in the child. Furthermore, other studies have shown such associations. This data requires more searching review for hidden problems.

h. Anemia:

Gershon, Lawrence E., Churchill, John A., Berendes, Heinz W. Anemia in gravida has been regarded as an indicator of nutritional, especially protein, impairment. However, we have failed to demonstrate any significant association between rather severe anemia in mothers and developmental failures in the offspring.

Classification of anemias did not clarify the picture. Perhaps anemia, while related to iron intake, is decoupled from protein intake.

This study and other problematic ones like it should perhaps be presented to Perinatal Research Committee, Project Directors and their associates for fresh ideas and approaches.

i. Twin Study:

Willerman, Lee, Churchill, John A., Shakhashiri, Zekin A. Hypothesis: Twins have lower birth weights and IQ than singletons. Study confirms the hypothesis, and has progressed to the stage of final analysis for publication. The thesis is that the human mother often cannot adequately supply nutrients to two fetuses.

Within the study, we have also tried to confirm our previous findings that the smaller of identical twins has the lower IQ. In this we failed. The reason appears to lie in use of the 4-year IQ as the outcome measure. We found the correlation coefficient, r, of IQ within identical twin pairs was 0.7. This value is not characteristic of other findings of 0.9. Variance of the smaller twin was also excessively great for reasons we cannot at the moment explain.

Group 2 Studies:

Series of studies on Mechanical Factors of Delivery:

This series of studies proceeds to test the spatial theory of differential cerebral impairment from trauma at birth.

The studies are complex because of effects of interaction of several factors, including force of uterine contraction, gradient of pressure changes with rupture of membranes (Schwartz), head size, malleability, and strength of skull, pelvic capacity, diameters and configuration, position of head in pelvis including asynclitic tendencies, torque force exerted on head, and use of forceps. We need help from obstetricians in evaluating these matters.

1. Relationships of IQ to head position at birth:

Churchill, John A. and Willerman, Lee. Children born LOA were found to have higher IQ than those born ROA. (Presented at the Conference on "Physical Trauma as an Etiological Agent in Mental Retardation", Lincoln, Nebraska, October 13-16, 1968.

2. Relationship of clinically measured pelvis and IQ:

Willerman, Lee and Churchill, John A. Differences were found in 4-year IQ between children born of mothers with large as compared with those born of mothers with small pelves. (Presented at conference on "Physical Trauma as an Etiological Agent in Mental Retardation" Lincoln, Nebraska, October 13-16, 1968.)

3. Relationship of X-ray Pelvimetric measures and Weshsler IQ of Child.

This study is the most appropriate and while trends toward significance in the findings are apparent now, further study must await accumulation of more 7-year IQ data. Small differences must be expected in as much as most cases found to have rather small pelvic measurements by x-ray are sectioned thus removing the most jeopardized subjects from the study.

4. Breech Delivery of full-term infants:

Churchill, John A. No difference in 4-year IQ or 8-months' development scores has been found in a comparison of breech-born to LOA-born children.

A possible difference in frequency of convulsive seizures and electroencephalographic abnormalities is being studied.

I would enjoy the assistance of Fernando Torres in EEG aspects of this Study once something worth his time becomes apparent.

5. Retinal Hemorrhage:

Rosenbaum, Arthur L. The idea was conceived that retinal hemorrhage might occur as a result of distention of retinal veins, secondary to compression of the brain and its drainage veins during descent of the fetal head. In cases with unilateral retinal hemorrhage, the eye affected might relate to the head position at birth in the manner found for previous EEG, focal epilepsy, and IQ studies. If the hypothesis were supported, further understanding of mechanism of differential cerebral impairment would be gained.

Evidence has developed that supports the hypothesis, but it is highly desirable to increase the case numbers.

Recently, Dr. Green, New York Medical, has started a study on retinal hemorrhage which, however, does not bear in any way upon the hypothesis posed by Dr. Rosenbaum. We have been wondering whether Dr. Green would like to collaborate with us in this study, once he had cleared through work of his own.

Group 3 Studies:

Hematocrit in Prematures:

1. Low hematocrit in spastic diplegia of prematurity.

Churchill, John A., Carleton, Jack and Berendes, Heinz W.
This has proceeded from a study of all cases identified as spastic diplegia or mild spastic diplegia among all births of 2.0 Kg. or less.

Spastic diplegics were found to have lower hematocrits in the first 5 postnatal days than non-spastics. (Reported at Academy of Cerebral Palsy, December 1968, Florida).

2. Low Hematocrit in Prematures with Cerebral Hemorrhage:

Carleton, Jack and Churchill, John A. Premature babies having low hematocrits and dying in the first 2 weeks were found to have cerebral hemorrhage more frequently than similar infants with high hematocrits.

The findings suggest that spastic diplegia may be caused by cerebral hemorrhage. Reported at Academy of Cerebral Palsy, December 1968, Florida.

3. Consideration of Etiological Factors in Spastic Diplegia or Prematurity:

This work is an extension of the previous work to include other presumptive etiologies. Among findings are: spastic diplegia occurs in true prematures and not in small-for-dates babies; low hematocrit from hemolytic anemia is not associated with diplegia; spastic diplegia occurs in Cesarean Sectioned gravida where the reason for section is not relevant to threatening situation for the child.

Knowing of Dr. Masland's keen interest in the spastic diplegia problem, I would like to enlist his help in this Study, which requires extensive knowledge of the literature which he has reviewed.

Miscellaneous PRB Studies:

1. Drug Studies:

Churchill, John A. and Goldman, R. A series of four studies to determine whether a) phenothiazine, b) meprobamate, c) furadantin and d) diphenhydramine affected the fetus in terms of duration of gestation, birthweight, malformation, 8-month scales and 4-year IQ. No difference at all was found between subjects and controls in spite of the fact that mothers receiving one of the medications received significantly more kinds of other drugs as well.

2. High hematocrit:

Weinberger, M. and Goldman, R. This study is in rapid progress. Babies with high hematocrit tend to be postmature, have prolonged gestational age, have placental lesions, lower IQ ($p < .05$). The frequency of mongolism is high (even in absence of congenital heart defects).

3. Early Signs as Predictors of Death and Neurological Abnormality Among Premature Infants Weighing 1000 to 2000 Grams:

Joseph S. Drage, M.D. and Karin B. Nelson, M.D. Premature infants in this birth weight range have been studied to determine whether the presence of certain abnormal neurological signs in the nursery permits prediction of death in the first year of life or neurological abnormality at one year.

It was found that suck, grasp, tone and cry related significantly to death during the first year and to neurological abnormality at one year. This is also true for 5-minute Apgar score of four or less. The moro reflex was related significantly to the total death and neurological abnormality and to death alone and, less significantly, to neurological abnormality at one year. Infants in this birth weight range, reported to be tremulous or jittery during the newborn period, had a significantly increased chance for surviving in the first year of life. Combinations of signs (5-minute Apgar of four or less, grasp and suck) were compiled and the more of these three signs present in the newborn period, the higher the degree of undesirable outcome. (Paper presented at American Academy of Cerebral meeting in December 1968.)

4. Mortality and Morbidity Among Infants Weighing 1000-2000 Grams:

Joseph S. Drage, M.D. and Karin B. Nelson, M.D. It has generally been observed that for premature infants both death and neurological abnormality are inversely related to birth weight. The purpose of this study was to quantify this trend by a study of a group of very low birth weight infants, analyzed in 100-gram birth weight intervals; in effect, to expand the scale so that comparisons can be made within the birth weight range of 1000 to 2000 grams. Thus, we focused on a small part of the birth weight spectrum, a division which contains only a minor proportion of the births but a relatively large share of the mortality and morbidity.

Among this group of 1,364 liveborn infants, 917 infants or 67% were examined at one year, 20% died and 12% were lost to follow-up. The outcome was known on 1,191 infants and of this group 16% were neurologically abnormal at one year and 23% died during the first year. Among the 917 examined at one year, 21% were abnormal. Outcomes were then analyzed in 100-gram birth weight intervals between 1000 and 2000 grams. It was apparent that there was a marked variation regarding outcome within the birth weight range, with mortality and morbidity increasing as birth weight decreased. It was possible to quantitate mortality and morbidity by 100-gram intervals of birth. These outcomes are also being tabulated controlling on gestational age, maternal education, socio-economic index, housing density and race.

5. Early Signs of Neurological Abnormality as They Relate to 4-Year IQ:

Joseph S. Drage, M.D. and Richmond S. Paine, M.D. Among a group of Study infants weighing more than 2500 grams at birth and whose mothers had completed nine or more years of education, abnormalities of the following neurological signs were statistically significant when correlated with reduced IQ's. In the case of white infants, tone of neck flexors, tone of neck extensors and tone of lower extremities, asymmetrical stepping, asymmetrical plantar grasp, asymmetrical palmar grasp, abnormal blinking reflex were significant. Among Negro infants, the following signs were significantly correlated with low IQ's: convulsions, asymmetrical tonic neck reflex, absent moro reflex. Preliminary tabulations suggest that some abnormal neurological signs in the newborn period do in general carry an increased statistical risk of mental retardation on follow-up examination at four years of age. (Presented by Dr. Paine at XI International Congress of Pediatrics, Mexico City, December 1968).

6. Apgar Scores as Related to Psychological Examination Findings at Four Years of Age:

Joseph S. Drage, M.D. This study has matched one and five-minute Apgar scores of children to their performance on the 4-year Psychological examination. Children with certain congenital malformations have been excluded. Controls for the study are birth weight, education of mother, race, sex, the outcome on the 4-year psychological examination, as defined by the Binet IQ score, the Graham-Ernhart Block Sort test score, assessments of fine and gross motor development, behavior profile and the overall impression. Findings are now in the process of being evaluated.

7. Sudden and Unexpected Death:

Joseph S. Drage, M.D., Toshio Fujikura, M.D. Some 207 cases of sudden death among 36,000 Collaborative Study children where death occurred outside the Study hospital have been reviewed regarding the cause. The purpose of this study was to review the early neonatal period of infants later experiencing sudden, unexplainable death for evidence of abnormality or instability in the neonatal period which could differentiate these infants from a group of controls matched for institution, sex and birth weight. Data is being compared regarding the time of first breath, time of first cry, need for resuscitation, Apgar score at one and five minutes, staining of skin and umbilicus, need for special and environmental condition, temperature variation, abnormalities of cry, activity, respiration, color, feeding and the presence or absence of seizures. This data is being tabulated to test the hypothesis that children categorized as sudden unexplainable deaths have manifested in the newborn period signs

demonstrating instability which are not present in a matched control group.

8. One-Year Head Circumference in Relation to IQ at Four Years:

Karin B. Nelson, M.D., and Jerome Deutschberger, Office of Biometry. This study relates head circumference at one year to IQ at four years. The main variables are head circumference at one year, body length at one year and head circumference at one year by body length at one year. Control variables have been race, sex and education of the mother. The outcome variables have been 4-year IQ and the Graham-Ernhart Block Sort test.

9. Perinatal Factors in Congenital Heart Disease:

Lenore Bajda, Heinz Berendes, and John Sever of PRB, NINDS, and Sheila Mitchell, Assistant to the Director, NHI Presentations of preliminary findings on a study sample of 82, and then 112 definitely diagnosed congenital heart cases revealed the need to relate findings to specific cardiac lesions for a meaningful analysis. Since definitive cardiac diagnosis frequently involves observation of the course of patient and heart findings to 4-5 years of age and later, complete ascertainment of congenital heart cases in the collaborative study "core" population is an on-going process. The investigators have continued to add cases to the study population, using the 1964 cohort with follow-up at least to 1968 where indicated. At present there are 3 institutions not completely processed (that is, with a definitive diagnosis meeting study criteria). Ascertainment should be completed by July and data analysis and its report prepared shortly thereafter.

10. An Investigation into Relationships Between History of Signs, Symptoms and Behavior Early in Pregnancy and Pregnancy Outcomes:

Lenore Bajda, et al (presently indefinite) Preliminary design of this study was rejected. Discussions concerning redesign are presently underway with R. Holden, anticipating redesign and smaller sample will be acceptable.

11. Georgetown Retrospective Study on Mental Retardation - Phase II:

Data on a subsample of that used in the Phase I part of the study has been processed and tabulated. Analysis is underway. It is anticipated that a paper on this analysis will be completed before the end of the year.

Studies on non-PRB data - Contract with Department of Obstetrics, Wayne State University - Churchill, Moghissi, Syner and Frohman

1. Maternal amino-acid blood levels and developmental measures in offspring:

The hypothesis of this study is that blood amino-acid concentrations of gravida in the last trimester is positively correlated with birth weight, length and crainal volume of the baby. The study, now including well over 100 cases, supports the hypothesis. (paper accepted for publication by Amer. J. Obstet. Gynec.). Correlation coefficients on this data are being run and will be available for review. To be presented at meeting of American College of Obstetrics and Gynecology, April 28, 1969.

No association between dietary data and amino-acid levels or of infant measures could be found. Children are being given Bayley Scales at 8 months of age, but too few tests have been completed.

Chromatographic analysis of individual amino acids are being done. Twelve analyses have been done, the results of which look too good to mention yet. The next phase of the study will be to see if amino acid levels can be elevated by giving protein concentrates and if so whether the infant measures increase.

2. Amino Acid Assays on PRB Frozen Serum Samples:
Churchill, Berendes and Sever

Amino acid determinations on frozen PRB samples on cases with outcomes already known. This series of studies has been planned. The first study, which is aimed at relating individual amino acid concentrations in sera of cases and controls included in the acetonuria study, has been approved by the NINDS Directorate.

If the utility of frozen PRB sera for this purpose can be established, an enormous potential for use of the sera in association with other PRB data will be made available.

Laboratories in the collaborating or other institutions may wish to join in this effort if the proposed step is successful.

3. Protein Deprivation in Mice:
Churchill, Carleton, Hanson and Holley

a) We have run a study of protein deprivation in gravid C-57-B-6 mice obtaining small newborn progeny. Because of unexpected aberrant performance of this strain in the operant conditioning procedure, we obtained only weak ($p \leq .05$) evidence of learning deficits.

However, the main thrust of this study was to obtain brains for detailed histopathologic study. These brains are being studied. We expect to find minute changes at best, such as decreased cell size in forebrain, clumping or reduction in Nissl's substance, laminar losses, ghosting or satellitosis of layer IV pyramidal cells. Fuelgen stain may reveal deficits of nucleic acid moities.

b) A second study using a white mouse known by us to condition well in the particular apparatus used is underway.

c) It is proposed to explore systematically diets lacking in essential amino acids in combination and singly.

II. PROBLEMS

The activities of the Section on Pediatric Neurology have been oriented to solve the problems reported in the Annual Report covering the year through June 30, 1968. Considerable effort and time has been spent to arrive at anintegrated systematic and comprehensive method of analyzing data so that separate studies can be directly compared to each other. Aims have been to simplify and strengthen the procedure of data analysis.

Procedures have been drawn up for defining cohort, a matching program for statistical analysis and a program for equating numerous control and procedural variables has been described.

III. PROPOSED FUTURE OBJECTIVES:

1. Through assistance to the Chief, Perinatal Research Branch, and others, to accomplish as soon as possible development of a definitive data analysis plan;

2. Thereafter, to promptly initiate an active attack on analysis of data, oriented to elucidate associations between maternal factors and neurologic and psychologic outcomes of the children;

3. To cooperate with the Chief of the Perinatal Research Branch in meaningful collaboration with Project persons on segments of analysis of data; and

4. To explore the possible utility of stored serum samples for integrating amino acid and other chemistry with appropriate studies of maternal factors as related to outcomes in children.

IV. MISCELLANEOUS:

Contract Work:

1. Contract with Wayne State University on the Study of amino acid concentration in maternal blood as associated with birth, length and cranial volume of offspring. This work is progressing well. A

preliminary paper has been accepted for publication by the American Journal of Obstetrics and Gynecology. A second, extensive, paper will be presented at the Annual Meeting of the American College of Obstetricians and Gynecologists in May, 1969.

Analysis of individual amino acids in blood samples is now being done. The result on 12 cases is at hand. 8-month Bayley tests are being performed, there now being a total of about 50.

2. Contract with Dr. Roberto Caldeyro-Barcia, Montevideo, Uruguay, for a fetal physiologic work.

This project was reviewed on April 22, 1969 with Dr. Caldeyro-Barcia who was visiting here. He has submitted vouchers for the past several months' completed work. His work is progressing well. The only problem being a current deficit in case numbers as previously projected. He has been obtaining interesting electroencephalic recordings, which are simultaneously recorded with other measures of fetal physiologic status.

C. SECTION ON BEHAVIORAL SCIENCES

Report for the period July 1, 1968 through June 30, 1969

I. SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACCOMPLISHMENTS

A. Research Findings and Areas Under Investigation

1) Of 213 children born at Boston Lying-in, those delivered in the right occiput anterior position earned significantly lower Stanford-Binet IQ's at four years of age than those delivered from the left occiput anterior position. This relationship held despite the application of forceps. (Willerman and Churchill)

2) Two hundred eighty-seven children of vertex births whose mothers were coded as having borderline or contracted pelves had significantly more frequent low IQ's (below 86) at four years of age than 243 children whose mothers had adequate pelves. (Willerman, Churchill and Rosenbaum)

3) Children born of small pelvis mothers, as compared to children born of large pelvis mothers, had significantly lower IQ's at four years of age. Children born of these small pelvis mothers who had been delivered by forceps made more errors on the Tactile Finger Recognition Test at seven years of age than those children of large pelvis mothers who were delivered by forceps. (Willerman and Churchill)

4) Among 3,000 white children, it was found that the four year IQ of those who were in the lowest quartiles on the Bayley Mental and Motor Scales administered at eight months of age, depends strongly on the socioeconomic class of the child. The higher the socioeconomic status, the less impaired the child. However, for children scoring in the upper quartiles at eight months, there is little association between socio-economic status and IQ at four years. (Willerman, Sledge and Fiedler)

5) A directory of control cases for selected outcome variables is now available. It consists of two parts: (1) means, number of cases, standard deviations and variances for all possible crosses of race, sex, institution and SE index for selected outcome variables; (2) outcome variables falling into each of the above cells by individual NINDS numbers. (Willerman)

6) Offspring from Negro-white matings (n=171) were individually matched to children from white-white and Negro-Negro matings on hospital of birth, socioeconomic index, and marital status. Though not significantly different from the controls in either length or weight at birth, by four months of age the interracials were significantly smaller than the controls. At one year the interracials were still smaller, but the magnitude of the differences had diminished considerably. On psychological test performance at eight months, no differences were observed. At four years the IQ's of the interracial children were significantly lower than the white controls, but not significantly lower than the Negro controls. Birth-weights and lengths of the interracial children were intermediate to the

larger white and smaller Negro children regardless of the race of the interracial mother. (Willerman, Naylor, Myrianthopoulos and Churchill)

7) Consanguineous matings have been reported to be associated with a higher incidence of fetal and neonatal mortality as well as mental retardation in the offspring. The present study will examine outcomes in the offspring of 148 sets of parents in the Collaborative Study who are second cousins or closer. The hospital records of these cases have now been identified and are currently being abstracted. (Willerman, Myrianthopoulos and Naylor)

8) Previous research by others has suggested that during labor the head of the fetus in vertex delivery is subjected to far greater mechanical pressure after membrane rupture than before. We are currently awaiting a print-out of infant developmental measures and IQ scores as a function of interval between membrane rupture and birth. (Willerman, Rosenbaum and Churchill)

9) The hypothesis to be tested is that the magnitude of the difference in four year IQ between children of high socioeconomic status and low socioeconomic status will be significantly greater among abnormal infants than their matched controls. The present study attempts to assess the effects of SES as a possible influence on the outcome of neurologically and psychologically impaired infants. (Holden and Willerman)

10) This study evaluates the relationship of children dysfluent in speech at age three, and earlier attitudes of their mothers as reported on the Parental Attitude Research Instrument (PARI) obtained when the child was eight months old. A randomly selected group of children matched for age, sex and race but with no dysfluent behavior will serve as controls. (Holden and LaBenz)

11) The relationship of selected demographic, perinatal and other developmental characteristics of some 13,000 children to their intellectual and motor performance at four years of age is being investigated. Preliminary findings show that: (1) Differences among white, Negro and Puerto Rican children in IQ, socioeconomic index, educational level of mother and sex ratio are highly significant; (2) Highly significant differences by ethnic group in percent pass occur on all items of the Stanford-Binet between test levels II-6 and VI years; (3) Among both whites and Negroes highly significant differences in SE index and in education of mother between those who pass and those who fail occur on all Stanford Binet items examined. This relationship is much less pronounced among Puerto Ricans; (4) Sex differences in favor of the female occur on approximately 50 percent of the Binet items among both white and Negroes. Again this relationship is less pronounced among Puerto Ricans. (Sledge, Khanna and Weber)

12) In an investigation of the relationships among birthweight and gestational age and mental and motor performance at eight months and IQ at four years the following preliminary findings have been made: (1) Four year IQ increases with both birthweight and gestational age

when these relationships are controlled for ethnic group, sex and education of mother; (2) four year IQ increases with educational level of mother when controlled for birthweight, gestation, ethnic group and sex; (3) four year IQ increases as eight month mental and motor scores increase when controlled by ethnic group, sex and education of mother. (Sledge, Deutschberger, Berendes and Dowling)

B. Data Collection

From the period 7-1-68 to 4-30-69, 4526 four year psychology examinations have been received in the section. Projected to 6-30-69, 5528 such examinations will have been received. As of 4-30-69, 4053 four-year examinations have been processed (edited). The current backlog of these examinations is 828.

From the period 7-1-68 to 4-30-69, 4529 seven year psychology examinations have been received. Projected to 6-30-69, 5540 such examinations will have been received. As of 4-30-69, 5750 seven year examinations have been processed. (edited) The current backlog of these examinations is 6041.

C. Interinstitutional Quality Control

Eighteen quality control trials are scheduled each year in which institutions are paired, and psychologists from visiting institutions retest a yearly total of 108 children previously tested in the home institutions with the 4 and 7 year psychology batteries. These retests are observed by a psychologist from this Section who then discusses the results with all of the psychologists involved. This procedure allows for resolution of discrepancies in methods of testing, scoring and handling children as well as providing test-retest reliability coefficients for the 4 and 7 year examinations.

II. PROBLEMS

The major problem is this section is the need for additional clerical help to process incoming examinations.

III. PROPOSED FUTURE OBJECTIVES

These are continued analyses of psychological outcome variables obtained at different ages in relationship to perinatal measures and to measures of developmental status collected by the other disciplins. Analyses of the interrelationships of the various psychological measures are also being planned.

D. SECTION ON INFECTIOUS DISEASES

Report for July 1, 1968 through June 30, 1969

I. SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACHIEVEMENTS

Large-Scale Serological Testing

Three types of studies are being conducted:

Broad serological approaches to identify the viruses which are infecting the study population.

Complete serologic testing for 8,000 pregnant women for 5 antigens has been analyzed and is being prepared for publication. The antigens included influenza A, herpes simplex, mumps, cytomegalovirus and rubella. The analysis includes comparison of the outcomes of the pregnancies for these patients and matched controls.

Intensive studies of important infectious agents.

The frequency of cytomegalovirus infections in newborns was determined to be approximately 3 per 500. These children are being followed longitudinally to identify possible associated defects. Another investigation of cytomegalovirus is being conducted with serial specimens taken from pregnant women throughout pregnancy and from the children at birth to determine the possible association of time of infection and pregnancy outcome.

The frequency of perinatal toxoplasmosis and the associated effects, including congenital toxoplasmosis, microcephaly, low birth weight, have been identified for a study population of 23,000 pregnant women. Related variables such as maternal age and race are being analyzed in conjunction with the data for the pregnancy outcomes.

Selected studies of pregnancies with abnormal outcomes and matched controls.

Groups of patients with congenital heart disease, abortions, stillbirths, neonatal deaths, mongolism and malformations of the central nervous system and other systems have been identified as serologic tests have been completed for many of these groups along with matched controls to determine the possible influence of virus infections in relation to these outcomes.

Research on the development of the new antigens for the Australian antigen (hepatitis) and EB virus (infectious mononucleosis) was carried out. Their use in the study of pregnant women in the Collaborative Perinatal Research Study is proceeding and these antigens will be added to the regular testing in the near future.

Virology - Tissue Culture

Cytomegalovirus has been isolated routinely in WI-38 tissue cultures as well as MA-184 and additional new cell lines which have been selected for this purpose. A comparison of antibody determinations with several different methods for rubella has shown that there is some disagreement between the HI and neutralizing antibody titers. This data has been reported. Rubella has been isolated from explant tissues in much greater frequency than from simple homogenized tissue specimens. The usefulness of this technique permits the detection of very small amounts of residual rubella virus in tissues. Fluorescent antibody studies of infected tissues is also proving to be a very sensitive method for detecting immunoglobulins and residual virus in tissues.

Experimental Animals

Pregnant rabbits were found to develop congenital infection and runting was detected in a number of babies. In addition, cataracts occurred at a low frequency. It appears that disseminated infection in the developing fetus is responsible for these effects. Comparisons with vaccine strains show that the vaccines do not produce infection in the rabbit and thus transmission does not occur.

Pregnant monkeys inoculated with vaccine strains at various times in gestation do not show transmission of the virus to the developing fetus, whereas wild strains do transmit.

Immunology

High antibody titers to measles have been found consistently in patients with subacute sclerosing panencephalitis. One of the outstanding contributions of the Section was the isolation of measles virus from the brain tissue of a patient with subacute sclerosing panencephalitis. This procedure was accomplished with the use of a mixed culture technique employing HeLa cells.

Suppressed chronic measles infection of the central nervous system was studied with virus isolation as well as immunological procedures. Rubeola antigens were found in the brain of mixed cell cultures. However, complete infectious virus was only detected in the mixed cultures. The rubeola virus, while antigenically identical to other strains of rubeola shows extensive adaptation to tissue culture and high titers of the virus are produced in essentially all tissue cultures with this strain.

Vaccines and Field Studies

Vaccine studies with the Gilchrist P-48 strain vaccine showed this to have characteristics similar to HPV-77 and Cendehill. There was shedding of virus from the vaccinees and high titers of antibody developed. The administration of HPV-77 grown in WI-38 intranasally into volunteers did not result in infection. This data further indicates the probable safety of administration of this vaccine to children who are in contact with women of childbearing age.

Field studies on the epidemiology of toxoplasmosis in Puerto Rico were initiated. These studies represent extension of the observations in the Perinatal Research Study of the high frequency of antibody and seroconversions among women of Puerto Rican background. The main emphasis of the current studies is on the mode of transmission of the infection and the frequency of perinatal infections with toxoplasmosis.

Studies on H-1 and H-3 viruses suggested a low rate of infection among women during pregnancy. Possible isolations from fetal tissue have been noted.

Mycoplasma Infections

Mycoplasmas were isolated from approximately 15% of spontaneous abortions in studies conducted with material from Kaiser Hospital in Hawaii and the Naval Medical Center. The high frequency of vaginal infections must be considered however and further studies on the isolation from the organs of fetuses are in progress. Experimental studies in a variety of animals show that vertical transmission of mycoplasmas do occur and investigations in primates are in progress.

Epidemiology

The epidemiology of rubella in the Perinatal Study was determined for the epidemic period and compared to the intervals before and after the 1964 epidemic. The association of rubella in the second trimester with fetal defects was suggested by the data from the Perinatal Study and has been reported. Further information of this type has come from a similar epidemiologic review of the Collaborative Perinatal Research Data at Johns Hopkins. Other studies on the relation of bronchodilators to asthma, the association of inguinal hernias and rubella, the relation of toxoplasmosis and parasitic infections, frequency of toxoplasmosis and syphilis, frequency of herpes simplex in relation to cancer of the cervix and the relation of neoplastic diseases to virus infections have been initiated.

Cytogenetics - Herpes Infections

Cytogenetic studies indicate abnormalities in association with subacute sclerosing panencephalitis. Studies of herpes simplex infections suggest high rates of infection with vaginal herpes in association with cancer of the cervix. The possible effectiveness of interferon or interferon-like mechanisms in the prevention of pathological effects relating to herpes have been studied.

Multiple Sclerosis and Subacute Sclerosing Panencephalitis

The work of Dr. Horta-Barbosa resulted in the isolation of measles virus from patients with subacute sclerosing panencephalitis. This finding documents for the first time that a common virus infection is capable of producing a progressive disease of the central nervous system. Additional work now indicates that the virus is biologically highly adapted to growth in tissues and has other characteristics which distinguish it from wild

measles virus. The immunologic deficiencies of patients with this disease are being explored in great detail at the present time. It appears that while the gut associated immune mechanisms are highly efficient and active, as is the interferon response, the patients may be exhibiting a specific defect in thymic associated immune mechanisms. Special collaborative work with Dr. King Engel and Dr. John Fahey is now in progress to determine further information on immune deficiencies which may be present in these children. Studies of siblings have failed to show any evidence of deficient immunity as have similar studies of parents.

Utilization of the same techniques that are now being employed for SSPE have been initiated with fresh material from patients with multiple sclerosis and other diseases of the central nervous system. Biopsy materials are being provided from a number of collaborators as well as from the National Institutes of Health. Serologic surveys of these patients have also been extended to determine possible associations with virus infections. Experimental animals have been inoculated as part of this testing program. Only fresh specimens are utilized and viable preparations are established in each case.

II. PROBLEMS

Lack of Funds for Materials Necessary for Studies

Because of the reduction in the research and development contract funds for virus reagents this year, it has not been possible to prepare many of the important antigens for testing. This has resulted in a restriction of testing performed.

Insufficient Personnel

We continue to be severely limited by the lack of sufficient positions for technicians, secretaries, Serum Center personnel, and statistical clerks. A minimum of six additional positions are necessary for efficient utilization of serum and antigen. This is particularly necessary because an increasing percentage of sera has demonstrated marked deterioration. Only through efficient utilization of procedures which are available will it be possible to obtain information concerning the exposure of patients to viruses and the importance of this exposure to the production of abnormal infants.

Variable Antigenic Preparations

It is apparent that the biological systems involved in producing the antigens are frequently not reproducible. Frequent changes in procedures, changes in tissue or special methods of concentrating antigenicity are necessary to obtain a new lot of antigenic material. In other cases anti-complementary effects must be eliminated or the antigens may have to be remade. The production of antigens requires individual research and development.

III. PROPOSED FUTURE OBJECTIVES

Experimental Animals

Further investigations will be conducted with experimentally infected pregnant and nonpregnant animals to provide direct information on routes of infection, pathogenesis, and possible methods of prevention of defects in the fetus due to infectious agents. Experimental animal studies will continue in pregnant monkeys obtained under contract arrangements. Viruses under study will include rubella, mumps, and cytomegalovirus. Brain specimens from patients with subacute sclerosing panencephalitis, multiple sclerosis and amyotrophic lateral sclerosis will be included.

Specimen Collection

Specimen collection has been increased to include tissue samples from placentas and abortuses at the Kaiser Hospitals in California and Hawaii so that the isolation of viral agents may be utilized to confirm and extend the serological findings. Simultaneous cytogenetic studies will be performed. Special fetal specimens will be studied from patients with abortions.

Cytogenetic Studies

The laboratory for cytogenetic studies will be expanded to work in conjunction with the infectious disease studies of abortion. This laboratory will include one additional technician and an animal handler.

Large-Scale Testing

Serological studies involving 30,000 specimens from pregnant women in the Collaborative Perinatal Research Branch will be continued. Cord sera IgM and IgA levels will be determined. Supplemental sampling of the study population will be necessary to include patients who register early in the first trimester of pregnancy so that documentation of virus experience in this period will be possible.

Antisera Production

Prototype sera will be prepared for 20 viruses for control testing.

Antigen Production

In the absence of additional support, ways will be sought through reductions of other activities to free funds to obtain antigens for rubella, cytomegalovirus, varicella, and new viruses which will be prepared and incorporated into the testing program. Several new bacterial and protozoal antigens will be added to the routine testing of the study sera.

PAPERS PRESENTED AT MEETINGS AND TALKS GIVEN BY SECTION PERSONNEL

July 1, 1968 - June 30, 1969

1. Perinatal Toxoplasmosis - Clinical and Serological Studies. 8th International Congress on Tropical Medicine & Malaria, Teheran, Iran, September 7-15, 1968. Dr. John L. Sever.

2. Vaccines: Past, Present and Future. First Lewis W. Sauer Lecture, Evanston Hospital, Evanston, Illinois, September 19, 1968. Dr. John L. Sever.

3. Primate Paradise. NINDS-PRB Research Seminar, National Institutes of Health, Bethesda, Maryland, October 2, 1968. Dr. William T. London.

4. Infectious Agents & Fetal Disease. Symposium on Fetal Growth & Development, San Diego, California, September 19, 1968. Dr. John L. Sever.

5. Adverse Fetal Outcome Following Maternal Rubella After the First Trimester of Pregnancy. Vaccine Contractors Meeting, National Institutes of Health, Bethesda, Maryland, October 15, 1968. Dr. John L. Sever.

6. Cytomegalovirus. National Naval Medical Center, Bethesda, Maryland, October 17, 1968. Dr. John L. Sever.

7. New Slow Viruses. Children's Hospital, Washington, D. C., October 21, 1968. Dr. John L. Sever.

8. Possible Exogenous Antigens in Multiple Sclerosis as Suggested by Serological Studies. Symposium on the Possible Role of Immunology in Multiple Sclerosis, Rye, New York, October 30, 1968. Dr. John L. Sever.

9. Cytomegalovirus Infections in Newborn Infants. APHA meeting, Detroit, Michigan, November 1968. Dr. Gary Birnbaum.

10. Infectious Diseases. Children's Hospital, November 15, 1968. Dr. John L. Sever.

11. Disagreements in Antibody Determinations. 23rd Symposium on Microbiological Standards, November 1968. Dr. David A. Fuccillo.

12. Congenital Rubella in Rabbits. 23rd Symposium on Microbiological Standards, November 1968. Dr. David A. Fuccillo.

13. Perinatal Infections, Immunoglobulins and Antibody. XII International Congress on Pediatrics, Mexico City, Mexico, December 2, 1968. Dr. John L. Sever.

14. Cytomegaloviruses. D. C. General Hospital, Washington, D. C., December 17, 1968. Dr. John L. Sever.

15. Epidemiological Study of Viral Diseases in Infants. Johns Hopkins Hospital, Baltimore, Maryland, February 6, 1969. Dr. John L. Sever.

16. Epidemiological Observations of Rubella in the Collaborative Perinatal Research Study. II. Clinical and Laboratory Findings in Children Through Three Years of Age. International Conference on Rubella Immunization, National Institutes of Health, Bethesda, Maryland, February 18-20, 1969. Dr. John L. Sever.

17. Perinatal Infections. Johns Hopkins Hospital, Baltimore, Maryland, February 25, 1969. Dr. John L. Sever.

18. Rubella Vaccine. University of Tennessee, Memphis, Tennessee, March 11, 1969. Dr. John L. Sever.

19. Rubella Vaccine. Memphis Pediatric Society, Memphis, Tennessee, March 11, 1969. Dr. John L. Sever.

20. Isolation of Measles Virus from SSPE Brain Biopsies. Dr. Luiz Horta-Barbosa.

21. Protection by an Interferon Inducer. Dr. Louis Catalano, Jr. Veterinary Virus Research Institute, Cornell University, Ithaca, New York, March 11, 1969.

22. Rubella & Rubeola. Tulane University, New Orleans, Louisiana, March 17, 1969. Dr. John L. Sever.

23. Isolation of Measles Virus from SSPE. University of Tennessee, Memphis, Tennessee, February 1969. Dr. Luiz Horta-Barbosa.

24. Epidemiology of Rubella & Rubeola. Tulane University, New Orleans, Louisiana, March 18, 1969. Dr. John L. Sever.

25. SSPE: Isolation of Measles Virus from the Brain, Federation of American Societies for Experimental Biology, Atlantic City, New Jersey, April 13-18, 1969. Dr. Luiz Horta-Barbosa.

26. Protection by an Interferon Inducer: Experimental Herpes and Encephalomyocarditis Virus in Mice. Federation of American Societies for Experimental Biology, Atlantic City, New Jersey, April 13-18, 1969. Dr. Louis Catalano.

27. Rubella and Rubeola. Course on Virus Infection of the Central Nervous System, American Academy of Neurology, Washington, D. C., April 22, 1969. Dr. John L. Sever.

28. Multiple Sclerosis and Viral Antibodies. Course on Neuroepidemiology, American Academy of Neurology, Washington, D. C., April 23, 1969. Dr. John L. Sever.

29. Suppressed Chronic Measles Infection of the Central Nervous System. Society for Pediatric Research, Atlantic City, New Jersey, May 3, 1969. Dr. John L. Sever.

30. Rubeola Antigen Development in Brain & Mixed Cell Cultures from Subacute Sclerosing Panencephalitis Patients. American Society for Microbiology, Miami Beach, Florida, May 4-9, 1969. Dr. David A. Fuccillo.

31. Congenital Rubella in Rabbits. American Society for Microbiology, Miami Beach, Florida, May 4-9, 1969. Dr. William T. London.

32. Recent Advances in Rubella. Northern Virginia Obstetrical Society, Fairfax, Virginia, May 8, 1969. Dr. John L. Sever.

33. Virus Infections in the Perinatal Period. Suffolk County Pediatric Society, Huntington, New York, May 12, 1969. Dr. John L. Sever.

34. Symposium on Immunological Responses to Perinatal Infections, National Institutes of Health, Bethesda, Maryland. May 20, 1969. Dr. John L. Sever.

35. Measles as a Slow Virus. NIAID Grand Rounds, National Institutes of Health, Bethesda, Maryland, May 28, 1969. Dr. John L. Sever.

36. Suppressed Measles Infection in SSPE. NINDS-PRB Research Seminar, National Institutes of Health, Bethesda, Maryland, June 4, 1969. Dr. Luiz Horta-Barbosa.

37. Immunological Aspects of Viral Diseases. Course on Virus Infections of the Nervous System, American Association of Neuropathologist, New Haven, Connecticut, June 21, 1969.

38. The Effect of Clostridium perfringens on Germfree Guinea Pigs. Conference of Research Workers in Animal Diseases, Chicago, Illinois, December 2, 1969. Dr. David L. Madden.

E. SECTION ON PATHOLOGY

Report for the Period July 1, 1968 through June 30, 1969

I. SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACCOMPLISHMENTS

A. Project Material

1. Laboratory Processing

a. CNS Project Material

To date 1,124 CNS specimens have been received and processed, so that any case can be ready for final evaluation within four days of requesting. Three-hundred and five cases have been completely processed histologically. A number of cases have been evaluated for specific investigations but not discussed in general review conference. The gross dissection of neuropathological specimens has previously been done. The work has continued on detailed microscopic study of the material resulting from submitted neuro-structures. The pace on this aspect of laboratory processing has increased with the addition of another neuropathologist to the staff in July 1968. An evaluation of gross and macroscopic photographs of all brains has been completed (748 cases).

b. Referred Human Material

Throughout the past seven years a number of Collaborative Institutions and investigators have submitted pertinent CNS specimens for macro and microscopic evaluations. These specimens are assigned a separate set of identifying numbers and processed by routine for Project material where feasible. These cases evaluated by Drs. Lipkin, Leventhal, Carleton, and Aparicio include fetal brains, congenital malformations, brain tumors, leukoencephalopathy and cases designated as cerebral palsy.

B. Data Processing

1. Condensed Data File

Although the SNOP system of coding has proved satisfactory and workable for the Section on Pathology, other disciplines or those unfamiliar with the system have expressed difficulty in retrieving SNOP-coded data from the data file. For this reason a summary data file was instituted for each autopsied death, each column being assigned to a specific category, with special emphasis on perinatal pathologic conditions. In malformed cases, the specific malformation is not coded but rather the case is

identified as being malformed. A column designated lethality of the malformation, another column indicates the presence and number of Group A malformation (see definition in congenital malformation paper by Froehlich and Fujikura) and another the presence and number of Group B malformations.

These data are up-to-date in the data file on the 1964 cohort. Abortions are excluded. In the process, a second look was taken at the autopsy reports and previous errors in coding and editing corrected. In addition, data obtained from other sources (birthweight, gestational age, race) were updated so that these were obtained from consistent sources (PED-1, AR-1 & PED-1, and AR-1 respectively).

2. Updating

Some autopsy protocols were re-reviewed in connection with the development of the condensed data file. Updating is closely related to the development of these files and serves as a check on previous coding.

Another activity was the follow-up of final inventories of outstanding material due but not yet received in the Section on Pathology. This inventory continued to have urgent priority within the Section during the past year. This is due to the phasing-out of the pathology portion of many of the Collaborating Institutions. It is necessary that appropriate requests for all outstanding material be placed with the responsible institutions as soon as possible. This will permit the completion of our material (as opposed to informational) files while such material is still available from the Collaborating Institutions.

C. Special Studies

1. Biologic Pattern Data Processing

Phase II of this project was re-evaluated, and may be briefly characterized as a "fleshing-out" of LISP-PAX into a more detailed and more (to the user) transparent system. This involves the input of increasingly detailed formal descriptions (initially in list structure form) of neuronal and nervous tissue structure from which effective picture grammars can be built. Higher level programs, i.e., portions of LISP-PAX, developed on the Q-32 are transferred to the PDP-10 and integrated with the already large body of analytic procedures developed by DCRT staff for image processing in general. At the same time, direct data and command transmission between the PDP-10 and the flexible scanner subsystem will have to be established.

In the spring of 1968 the work on the general purpose device was subjected to site visit and review by an ad hoc committee They reviewed the collaborative work with NBS and were apprised

of the defacto relationship to DCRT. They were fully apprised of the proposed use of the DCRT PDP-10 display system in furthering the general purpose device development.

As a result of a favorable report and recommendation of this committee, work on Phase II commenced in July 1968 the collaborative aspect with NBS being supported by contract. In addition to the programming, linguistics and logical structure work by the NBS Artificial Intelligence Group, the previously informal relations between PRB and NBS electrical engineers was formalized in order to speed completion of the flexible scanner subsystem.

The scanner-microspectrophotometer subsystem is now operational and includes a new stage controlled stepping motor, computer controlled fine focus, redesigned reference beam, log-ratio analog circuitry, modified scanner head and its electronics, nine-track magnetic tape drive with sophisticated programs for writing tapes of the results of scans in a format acceptable to the PDP-10, and a general purpose "J" box (circuitry to permit usage of I/O and interrupt characteristics of the LINC-8 in interfacing).

Expansion of the LISP-PAX system has proceeded in the area of tree structure manipulation and pictorial image processing functions.

The PDP-10 has been received and is in an acceptance testing phase. Currently, command and data transmission between scanner and computer is under exploration as well as transfer of LISP-PAX to the PDP-10 and its expansion by and integration with the already large body of image processing programs extant on the PDP-10.

In FY 1968 there was a Project Report for "Automated Microspectrophotometry Employing the LINC Computer," Serial No. NDS (CF)-66 PR/P 1354. It was incorporated during FY 1969 with Serial No. NDS (CF)-65 PR/P 1278.

2. The Length of the Umbilical Cord

The relationship between cord length and demographic variables as well as other parameters of fetal growth was studied using pooled Collaborative Study data. Although certain expected correlations were obtained, considerable variabilities were noted. In addition, institutional differences and inter-examiner differences in reporting made the pooled data difficult to evaluate. The study is discontinued. (Serial No. NDS (CF)-66 PR/P 1342)

3. The Neuropathological Study of a Series of Selected Monkey Brains from Animals in the Perinatal Period

This study of 103 selected perinatal monkey brains is designed to provide a morphological information base for experimental designs dealing with perinatal injury in primates. The protocol development and morphological observation has been postponed until facilities and experimentation can be established. (Serial No. NDS (CF)-66 PR/P 1352).

4. A Sequential Study of Ultrastructural Changes in an Experimentally Produced Traumatic Brain Lesion

The objective of this study is to provide timed data as to glial cell response to direct traumatic injury, employing initially mice. This will eventually provide a base for anticipated studies in primates. The technical problems have been completed and updated leaving only the histopathological evaluation to be completed. (Serial No. NDS (CF)-66 PR/P 1353)

5. Automated Microspectrophotometry Employing the LINC Computer

This project (Serial No. NDS (CF)-66 PR/P 1354) was incorporated during FY 1969 with Serial No. NDS (CF)-65 PR/P 1278.

6. Factors Influencing Quantitative DNA Staining

Further progress in this project concerned with the kinetics of staining and stain fading has been delayed due to the need to switch over from the LINC to the LINC-8 microspectrophotometer system. With the completion of the interface of the microspectrophotometer, work on this substantive project may resume in parallel to the scanner interfacing. (Serial No. NDS (CF)-66 PR/P 1355)

7. Congenital Malformations in Perinatal, Infant and Child Deaths

An analysis of congenital malformations in perinatal, infant and child deaths has been completed. (Serial No. NDS (CF)-68 PR/P 1649)

8. Placentation in Relation to Zygosity of Twins

The relationship between type of twin placentation and zygosity was studied in 569 sets of twins in the Collaborative Study. Perinatal death rates, birthweight, gestational age, birthweight differences, gravidity, and maternal age were evaluated in relation to twin placentation. (Serial No. NDS (CF)-68 PR/P 1650)

9. The Ultrastructural Evaluation of Developing Hyaline Membranes in Strain A Mice

Sequences of seven strain A six-week-old mice were placed in a specially constructed positive pressure high oxygen cage and one animal removed every 24 hours. The animals were killed and the lungs removed, fixed and processed by the large epoxy section technique. Comparisons between light and electron microscopic findings were to be made. The study is temporarily discontinued. (Serial No. NDS (CF)-68 PR/P 1651)

10. Ultrastructural and Histochemical Evaluation of the CNS in Mice Progeny when a Protein-Deficient Diet was Administered During the Second Half of Gestation

Initially 45 pregnant mice were divided into three groups and on the tenth day of gestation were placed on normal, low or high protein diet. After birth, normal diet was reinstituted for all and at 60 days of age the offspring were tested for learning ability using an avoidance apparatus. The animals were then killed and their brains perfuse fixed for either light or electron microscopic evaluation. Results of this preliminary study were inconclusive because of testing peculiarities for the strain of mice (C57/Bl) used. The investigation is now being repeated after selection of a mouse strain which shows reliable response to the test situation. (Serial No. NDS (CF)-68 PR/P 1652)

11. Correlative Light and Electron Microscopic Pediatric Pathology

The fundamental problem of light microscopic and electron microscopic correlation is dependent on the possibility of sequential examination of the same structures. In order to provide suitable standards for organs other than brain, Dr. Carleton was detailed for a six-month period to Ohio State University in order to collect and preprocess suitable tissues from a general pathology department. This first phase is completed with 61 general pediatric pathology cases and 40 surgical specimens collected. They are now being processed by this special technique and will be utilized as specific interest, desire for comparison of project material, and time permit. (Serial No. NDS (CF)-68 PR/P 1653)

12. Kidney Malformations in Fetuses of ACI/N Strain Rats

The rate of spontaneous genito-urinary malformations in ACI/N strain rats is being determined. Randomly selected pregnant rats are killed at or near term and the mothers and fetuses are being examined in detail for malformations involving the genito-urinary system. A preliminary report will be read at the Teratology Society Meeting to be held in Washington in July of this year. (Serial No. NDS (CF)-69 PR/P 1763)

13. Placental Study of Abortion Material (Obtained by an Induced Abortion)

A detailed histological review of induced abortion material is being undertaken by Dr. Fujikura in cooperation with the Department of Anatomy at Kyoto University in Japan. The collection of about 500 intact specimens is contemplated and it is hoped that collection will be completed by the end of this year. The material will be compared with the products of spontaneous abortions. (Serial No. NDS (CF)-69 PR/P 1764)

14. The Interrelationship Between Selected Congenital Malformations and Major Pathological Findings

The relationship between selected malformations in autopsied deaths and major pathologic factors in the baby as well as in the mother and placenta are being analyzed. (Serial No. NDS (CF)-69 PR/P 1765)

15. Reproductive Ability of the American Negro with Sickling and Its' Public Health Implication

The reproductive performance of 654 sicklers and 1,890 non-sicklers in the Collaborative Study was compared. The cumulative fertility rate of mothers with sicklemia was the same as that of non-sickling mothers. Because of evidence that mothers with sickle-cell trait have normal reproductive abilities, the gene will continue to propagate and a plea is being made that sickling tests be done on all Negroes. (Serial No. NDS (CF)-69 PR/P 1766)

16. The Clinical Significance of Circummarginate and Circumvallate Placenta (Extrachorial Placenta)

The clinical significance of completely circumvallate and completely circummarginate placentas was determined by an analysis of 39,514 gravida in the Collaborative Study. White women with completely circumvallate placentas had increased rates of antepartum bleeding, prematurity, and neonatal, infant and child deaths. Extrachorial placentas were more common in multigravidas. Despite associated difficulties, extrachorial placentas are uncommong and are rarely critical clinical problems. This paper is being prepared for publication. (Serial No. NDS (CF)-69 PR/P 1767)

17. Bipartite Placenta

An analysis of bipartite placentas of Project women at the Boston Lying-in Hospital is nearing completion. Bipartite placenta was associated with clinical problems such as antepartum bleeding and adherent placenta requiring manual removal, but the perinatal death rate was in the normal range. Older multigravidas were more numerous in the bipartite group, and a history

of infertility was more common compared to the total series. The paper is being readied for publication. (Serial No. NDS (CF)-69 PR/P 1768)

18. The Significance of Chorangiomas

A review of 84 histologically verified cases of chorangioma suggests an increased association with toxemia, hydramnios, erythroblastosis, fetal hemangioma, and single umbilical artery. There is a distinct female preponderance, and the condition is more common in whites. The prematurity rate in the surviving group is not different from that of single live births in the Collaborative Study. Analysis is proceeding and a paper will be prepared for publication. (Serial No. NDS (CF)-69 PR/P 1769)

19. Organ Weight/Brain Weight Ratiosas a Parameter of Prenatal Growth

The hypothesis that brain weight bears a fairly constant ratio to organ weight is being tested based on Collaborative Project autopsy material. Although autopsy weight is considered a reasonably reliable parameter of growth in conditions where somatic growth is not affected, it is unreliable in conditions of abnormalities of somatic growth such as diabetes, erythroblastosis and toxemia. The brain is postulated to be the reliable parameter in such instances. A series of regression analysis programs is being applied. (Serial No. NDS (CF)-69 PR/P 1770)

20. Viral Infection in Pregnancy and Congenital CNS Malformations in Man

Micro-complement fixation tests using 16 viral antigens and hemagglutination-inhibition test for rubella antibodies were performed on coded paired sera taken during pregnancy from 54 maternal cases with congenital CNS anomalies in their offspring and from 104 matched controls with normal babies. Results of this study failed to demonstrate a correlation between serological evidence of maternal viral infection during pregnancy and the occurrence of fetal CNS anomalies. (Serial No. NDS (CF)-69 PR/P 1771)

21. Pathologic Effects of Ligation of the Anterior Spinal Artery and/or the Great Radicular Artery in Monkeys

Spinal cords of monkeys which had been subjected to ischemia by means of surgical ligation of some of the arteries which contribute to their blood supply are under investigation. This is only one part of a major project, including a clinical and neuro-radiological evaluation of the animals done in collaboration with the Surgical Neurology Branch, IR, NINDS and the Medical Neurology Branch, IR, NINDS. All specimens have been processed and a histopathological evaluation is being completed. (Serial No. NDS (CF)-69 PR/P 1772)

22. Evaluation and Development of Neuropathology Special Staining Techniques

The purpose of this project is to compare and make modern practical application of multiple special staining techniques which although already contributed very much to the development of neuroanatomy and neuropathology, and still have a great potential, have been otherwise outdated by the incorporation of automatic methods and routines, as well as other modern procedures. Different varients of these techniques are being compared and the most advantageous ones are applied to fresh material as well as to specimens embedded in paraffin and in plastic, to be processed both for light and electron microscopic examinations. Experimental animals subjected to different neurological lesions are being used to test these techniques. (Serial No. NDS (CF)-69 PR/P 1773)

D. Other Activities

Dr. Lipkin has served as contract officer for the collaborative program with the Artificial Intelligence Group of the National Bureau of Standards as described in the Individual Project Report.

The Section Head continued his working relationship with the Image Processing Group, DCRT.

II. PROBLEMS

A. Problems in Processing of Forms

The lay editors and coders have had less time in the recent past to process the backlog of forms because each has been assigned new duties. However, the job of finishing this backlog has since April been given top priority.

As has been repeatedly mentioned in past annual reports, the Section has suffered from a chronic lack of personnel who could devote their efforts exclusively to processing Path-1, Path-2 and Path-3.

B. Tissue Processing

Much laboratory processing time was lost due to the move from our previous location and awaiting modifications of new laboratory facilities.

Considerable technical time was spent in training a histopathology technician as well as devoting time to the additional requirements for processing tissue of individual projects.

Lack of clerical or subprofessional personnel has been a chronic and major problem in the Section. Rapid phasing-out of pathology units in the various Collaborating Institutions continues to increase the demands on personnel. On the one hand, there are deluges of

slides and placental blocks arriving from certain institutions creating a problem of logging-in and filing. On the other hand, there seems to be considerable inertia in other institutions to submit outstanding required material, necessitating the use of other than the usual methods for obtaining the desired material. This requires extensive inventories for which additional clerical help is necessary. On occasion, this Section has had to supply assistance and information over and above what should be expected.

Another problem is that deaths, albeit few, continue to occur but as pointed out by one institution, there are no longer any Project personnel to perform the work with the result that the post-mortems have had to be done cursorily by non-Project personnel. Unfortunately these involve such conditions as chronic neurologic disorders, congenital malformations, tumors, etc. A provision still has not been made that these post-mortems be done with the same excellence as before.

III. PROPOSED FUTURE OBJECTIVES

Now that the move to new quarters has been completed, two new professionals have been added, the reorganization and integration of the Section into a functional unit has been achieved, the routine activities will now be data development from the now processed neuro and general pathologic material.

The Section will soon be in a position to begin the reaping of the return on the long and large investment in the image processing and microspectrophotometer projects, as well as that in the DCRT image processing facility. The various aspects of these heretofore separate projects are now approaching each other so that it may be possible to unify them in fact, as they have been from the beginning in concept.

Established research projects will be pursued as detailed in individual reports.

F. SECTION ON EPIDEMIOLOGY AND GENETICS
Report for the Period July 1, 1968 through June 30, 1969

I. SUMMARY OF SCIENTIFIC AND PROFESSIONAL ACCOMPLISHMENTS

During the past fiscal year the major effort of this Section has been in the continuation and expansion of the research activities; the creation of special files which would serve as sources for special genetic investigations; and the development of a comprehensive plan for analysis of the genetic and socioeconomic data of the Collaborative Study. Constant efforts have also been made to improve the quality of the data, to complete our data file and to obtain copies of missing records from the participating institutions.

The Section has continued to receive, edit and code information on the FHH-9 form. During this period approximately 6,000 FHH-9 forms were received and approximately 5,000 have been processed and sent to punch. In addition, 883 photocopies of missing GEN 5-8 forms have been retrieved from Philadelphia. These have been coded and verified and are now being processed for punching.

The results of our data analysis efforts have been extremely rewarding, as significant and meaningful findings emerged out of studies in progress. The epidemiologic survey of twins has been completed. The distribution of twins in the Collaborative Study population is as expected but the frequency of dizygotic twinning among Negroes was higher than among whites. Fetal and neonatal deaths amounted to 17.3% and were higher among like-sexed than unliked-sexed pairs. There was no difference in neonatal deaths between first- and second-born twins. An unusual and interesting finding was that the frequency of twinning was increased in higher socioeconomic groups. The twins are now being studied with regard to congenital malformations and other variables. Our study of the relation of medical and genetic factors to major congenital malformations has been extended to include a number of rare congenital malformations such as absence of abdominal muscles, agenesis of diaphragm, Poland's syndrome, congenital dislocation of the hip, microphthalmia and imperforate anus. Another study which takes advantage of the fact that many Study women had children by more than one mate, investigates the extent to which maternal factors are involved in the production of congenital malformations and other conditions of the newborn. In 152 cases with half sibships, six conditions were found to occur in high frequency among full and half sibs of the study child: Rh trouble, convulsions, congenital heart disease, club foot, mental retardation and polydactyly. In addition, a large number of half and full sibs showed different conditions and malformations. The study of genetic and socioeconomic factors in early and late fetal death is almost completed. Discriminant analysis of 1,877 early and late fetal deaths with respect to 40 medical, genetic and socioeconomic variables showed that toxemia, anemia and complications of pregnancy are good discriminants in both whites and Negroes; prior pregnancies and prior pregnancy wastage in whites only; and socioeconomic status in Negroes only. The study of placenta in relation to mother-fetus antigenic difference is also in the last stages of completion. Analysis of a large sample of

study data is consistent with the hypothesis that sensitization of the mother during pregnancy against paternal antigens leads to increased placental weight and increased birthweight in succeeding pregnancies. Arrangements are now being made for confirmation of these findings by laboratory studies.

A large number of studies of genetic and socioeconomic import is at varying stages of completion. Among the new projects initiated last year are: a study of congenital anomalies in siblings and other relatives of mongols; a study of the genetic significance of congenital abnormalities in the siblings and other relatives of children with cerebral palsy; sex chromatin screening of the population of a training school and subsequent investigation of patients with X-chromosome anomalies; and, an investigation of parental reaction to the realization of handicap in a child.

Two major concerns of the Section during the past year have been the development of special files for use in genetic studies which require specialized genetic methodology, and the development of a comprehensive plan for the analysis of the genetic and socioeconomic data collected in the Collaborative Study. Four special files are now being prepared and they are expected to yield important genetic information: the record linkage file which seeks to identify the relatives of gravidae participating in the study, through a record linkage system, making possible the construction of complete pedigrees and the undertaking of a wide variety of genetic investigations. At least 6,482 gravidae reported other registrants to be relatives; the consanguinity file which identified at least 148 gravidae, who reported themselves as mates of close relatives, 67 of first cousins, 81 of second cousins or more remote relations; the interracial mating file which identified 184 matings between white and Negro, resulting in liveborn offspring; and the twin file which contains 615 pairs of twins, most of whom can be followed to age 7 years.

A preliminary plan for comprehensive analysis of the genetic and socioeconomic material of the Study has been drawn up. This purports to explore ways and means of utilizing the maximum amount of data collected in the study with maximum efficiency and in broadest scope. To this end, we are bringing together a panel of genetic experts to help not only finalize such a comprehensive plan, but also to oversee its implementation. It is anticipated that a first meeting of this panel will take place early in the summer of 1969 and that the panel will meet periodically to review and guide the data analysis efforts.

The Section has participated in the quality control program and has prepared two evaluations of the FHH-9 form as it is being coded and verified. An analysis of the evaluated items has been sent to all institutions and it has been considered very helpful in maintaining a high quality of collected data. The Section has also conducted two workshops for the FHH-9 interviewers, at Philadelphia and Providence.

II. PROBLEMS

The main problem which this Section continues to face pertains to data analysis. One part of this problem is the shortage of trained professionals to analyze the mass of collected data, which has become critical with the current restrictions on hiring. Another part is related to problems in communication between investigators, systems analysts and programmers.

The shortage of trained people for analysis is aggravated by the heavy, administrative burdens imposed upon the professional personnel of the Section. Efforts have been made to meet this shortage, by inviting qualified research workers from outside the project to participate in the analysis of the genetic and socioeconomic material. It is also anticipated that when the advisory panel becomes functional it will help marshal additional resources for analysis. With regard to our own efforts in analysis, we urge that the investigator and the programmer be allowed to work together in all phases of computer processing without the interference of intermediates and without the hindrance of unnecessary administrative steps. We further urge that those professionals who have knowhow and talent in programming be encouraged to act as their own programmers.

III. FUTURE OBJECTIVES

The future objectives of the Section are: to strengthen our professional staff; to develop a comprehensive plan for the analysis of the genetic and socioeconomic material of the Collaborative Study and to implement such plan; and to create laboratory facilities for biochemical, genetic and cytogenetic investigations.

The achievement of the first objective will depend entirely on the removal of the present restrictions on hiring. The second objective is now being pursued vigorously. As mentioned earlier, a preliminary plan for genetic analysis has already been drawn and a panel of experts is being called to help further develop such plan and oversee its implementation. The last objective has been a source of constant embarrassment to this Section and its Head. The necessity for establishing these laboratories for special studies has been pointed out many times before (see previous annual reports) and was duly recognized to the extent that space for such laboratories was promised in the new NINDS-NIMH building. Yet after recruitment of well-trained professionals, the decision to establish these laboratories was reversed to the frustration of everyone concerned. We have no hesitation, however, in considering these laboratories as essential, and in listing them again among our future objectives.

IV. MISCELLANEOUS

A. Personnel

The personnel of the Section on Epidemiology and Genetics consists at

present of the following: professional, Dr. Myrianthopoulos, Head, Dr. Naylor, geneticist, Dr. Cowie, visiting scientist, Miss Baszynski, nurse-fieldworker, Miss Martin, statistician; other, one secretary, one clerk-typist, five coding clerks.

Dr. Glen Bartlett, our medical sociologist, left this Section at the end of June 1968, to complete his pediatric training at Stanford University. He has, however, maintained close contact with the Section and has worked on projects of which he started during his tenure here. We are greatly pleased to welcome to the Section, Dr. Valerie Cowie, from the MRC Psychiatric Unit, England, who joined us in October 1968, as a visiting scientist. Dr. Cowie is widely known for her work in the genetics of mental retardation.

B. Activities of the Section Head and the Professional Personnel

The Head of the Section, Dr. Myrianthopoulos, in addition, to his formal duties has carried out independent investigations in the genetics of neurological disorders, especially the lipidoses. Dr. Myrianthopoulos has maintained his affiliation with George Washington University as an Associate Professor of Neurology and Director of the Genetic Counseling and Research Center. In this capacity, he gives a series of lectures in the medical school and conducts genetic counseling upon referral by individual physicians. Dr. Myrianthopoulos is also a member of the faculty of the graduate program at NIH where in the past he has given a course in human genetics. Dr. Myrianthopoulos is a member of the Scientific Advisory Board of the Huntington's Chorea Foundation, a private organization which supports research in Huntington's chorea. He is also a member of the Committee upon Huntington's Chorea of the World Federation of Neurology.

In September, 1968, Dr. Myrianthopoulos attended the 12th International Congress of Genetics in Tokyo, Japan and gave a paper on his work on the genetics and demography of Niemann-Pick disease. In October 1968, Dr. Myrianthopoulos attended the meeting of the American Society of Human Genetics, in Austin, Texas, and gave a paper on his work with the twin material of the Collaborative Study. During the past year, Dr. Myrianthopoulos has also participated in many meetings and conferences and presented lectures to various scientific groups.

Since the changeover from grants to contracts in the Collaborative Study operations, Dr. Myrianthopoulos has served as Project Officer for Columbia University and New York Medical College. As such he has participated in contract negotiations, made recommendations concerning the budget, authorized payments, and made frequent visits to these institutions to discuss problems and assure the fulfillment of the contract terms.

Dr. Naylor has been instrumental in designing the analysis of many of the ongoing studies, often doing the programming, himself. He attended the meeting of The American Society of Human Genetics in Austin, Texas, October, 1968, where he discussed his work on mother-fetus antigenic

differences.

Dr. Cowie has been made a Clinical Associate in Neurology at The Children's Hospital of the District of Columbia, which among other benefits has facilitated her work on the investigation of parental reaction to the realization of a handicap in a child. In December, 1968, Dr. Cowie read a paper on Fertility and Chromosomal Changes in Parents of Mongols at the 12th International Congress of Pediatrics, in Mexico City. In January 1969, Dr. Cowie gave a lecture on cytogenetics at the University of London, England, for a postgraduate course for diploma in psychological medicine.

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G. SECTION ON DATA MANAGEMENT AND RETRIEVAL
Report for Period July 1, 1968 through June 30, 1969

I. SUMMARY OF ACCOMPLISHMENTS

This Section is entrusted with the task of receiving, coding, filing and storing forms in accordance with a system designed to facilitate form and/or data retrieval, as well as computer programming. The Acting Head of this Section has continued on detail from the Office of Biometry.

The total number of women registered in the 12 study institutions as of December 31, 1965 (the closing date for all such registrations) as adjusted was 58,831 -- of this number 56,193 were core study cases. Of the number of core study cases 53,749 have delivered with the last delivery on September 30, 1966.

Over 3.2 million forms will have been submitted by June 30, 1969. The available data from approximately 2.3 million forms has been processed into over 5.2 million punch cards in 111 card formats and converted into active computer tape files. The backlog in editing and coding consists of approximately 40,000 forms. 47,758 births have been reviewed at 1 year of age, 26,449 at 4 years of age and 8,091 at 7 years of age.

During the year work has continued in development and use of complete program packages to provide PRB controlled card update and editing to PRB operated master files and data banks, thus reducing dependence in this area on contract programming. In addition several standard programming packages have been developed during this fiscal year period for both studies and statistical analysis of data greatly facilitating this type of work previously done by other methods.

In addition to supporting the research activities of PRB with special information retrieval for case selection and informational tabulations, the Section has produced 150 sets of tabulations and large-scale studies involving large amounts of data, extensive systems analysis and complex data processing.

A continuing program of review of unaccounted study forms was performed with follow up contacts with all institutions planned with the objective of maximizing of all recoverable data for inclusion in the PRB master files and data banks. A quality review of file folders was initiated with systems development for organizing and binding of file folders which will facilitate their use while preventing loss or misfiling of individual study forms.

Development of a systems concept was initiated for a quality review of incoming data which is planned for program implementation as soon as all inputs are identified and defined.

II. PROBLEMS

Our problems are in two areas:

1) The objective of continuing the programming strength to permit more independence from outside programming has been limited by the current controls placed on hiring of new personnel coupled with the loss of personnel with no authority for their replacement. The Section, which contains large numbers of non-professional staff has continued shifts of assignment of personnel including retraining where required to meet program requirements, however this has been limited by shortages of personnel and skills required. Limitations on hiring of temporary personnel and use of part-time personnel to meet the needs of the Section will add to the difficulty of meeting objectives.

2) A basic problem which has continued has been the necessity of contracting for data processing services on an annual basis in lieu of every three to five year basis. Change of contractors can result in initial loss of effectiveness due to the learning process involved in the job order data processing requirements of the extremely large data bank of PRB.

III. PROPOSED FUTURE OBJECTIVES

It is planned to continue development of programming strength to permit more independence from outside programming needs. Having the input and file procedures set up and the data base relatively constant, sophisticated information retrieval-systems can be further developed to supply research needs more rapidly and accurately. The conversion and retraining of staff will continue so that present personnel can be reassigned to new current functions of the Section. New systems development are planned to be continued which will further effect reduced turnaround time on study requests as well as economy of operation. For example it is expected that the new Variable File System will be fully operational in the next fiscal year.

H. SECTION ON PROJECT SERVICES
Report for Period July 1, 1968 through June 30, 1969

I. SUMMARY OF ACCOMPLISHMENTS

Reading Room

Our collection of medical, statistical textbooks, scientific directories, atlases, annual publications of books and periodicals in print, etc. totals 784. In addition, there are 116 subscriptions to leading journals in the field of obstetrics, pediatrics, genetics, neurology, psychology, general medical sciences, nursing, public health, speech, language and hearing, etc. This figure includes 16 abstracting periodicals.

Our control file of medical, technical and statistical books in PRB sections, other than those housed in the Reading Room totals 1006.

Approximately 1407 visitors used the library and its facilities during the past fiscal year. Branch personnel borrowed 1926 books from the Reading Room.

Demand or Loan Service

The Medical Literature Unit processed, through NIH-NLM Library, 284 requests for books and journals not available in PRB Reading Room. Photocopy requests for articles procured from NIH-NLM Library for the various sections totaled 2,657; those reproduced in our xerox room totaled 5,661. Breakdown of distribution follows:

Office of the Chief	1003
Section on Behavioral Sciences	345
Section on Epidemiology & Genetics	611
Section on Infectious Diseases	874
Section on Obstetrics	1144
Section on Pathology	271
Section on Pediatric-Neurology	1011
Section on Speech, Language & Hearing	163
Medical Literature	2736
Miscellaneous	130
Office of Biometry	30
Total	8318

The Section also provides "Demand Service" for acquisition of literature from NIH Library which is urgently needed by PRB Staff and not available in PRB Reading Room. In most instances, the material is procured the same day.

Bibliography

This year a bibliography of Collaborative Perinatal Research Project Publications was compiled embracing pooled core data, local core data, and non-project studies of special interest to the authors at PRB. A subject index by title and an author index were included to facilitate use. It will be updated annually at the close of the fiscal year.

Semi-annual preparation of bibliography of Branch personnel for inclusion in Scientific Directory and Annual Bibliography, NIH, continues.

Work continues on the collection of reprints from the Collaborating Institutions. The references were listed in a bibliography prepared for the Lilienfeld Committee and included the following categories: Pooled core data publications, publications using Collaborative Project population, publications of personnel supported in part or in toto by Collaborative Project funds, and ancillary studies.

The following bibliographies prepared by MEDLARS and others, have been added to our collection since the last report:

Embryology and teratology
Retrolental fibroplasia
Rubella and rubella virus
Thalidomide
Viruses and congenital abnormalities
Anatomy and physiology of the cochlear and acoustic nerves
Rheumatoid arthritis and infectious diseases
Relation of occiput posterior and breech presentation to outcome of child
Oral contraceptives and blood coagulation
Nutrition
Nervous system diseases
Nutrition in pregnancy
Sleep cycles in the fetus, newborn and developing child
Specified aspects of rubella and rubella virus recurring
Smoking
Variables affecting psychometrics or intelligence tests
Mental retardation, etiological factors
Utilization Review - Selected bibliography of scientific, technological, attitudinal and organization forces that have been affecting health care systems and general society for a long time.
Speech therapists
Occurrence of selected viruses in humans
Body image as reflected in drawing of children
Dermatoglyphics
Parental attitudes towards children
Child development in relation to social class

Reprint File

Our collection is comprised of reprints acquired in literature searches for articles of critical interest to PRB Staff and pertinent to the Study. These are readily retrievable by author, subject and numerically and totals approximately 10,250. Subject headings utilized parallel those listed in Index Medicus.

Miscellaneous Activities

Dissemination of material and information in answer to a variety of inquiries and requests from the scientific as well as the lay community.

Compilation of special bibliographies as requested by investigators.

Periodical distribution of book lists, journals and abstracts and items of possible professional interest to PRB Staff, collaborators and others using our facilities.

Maintenance of a mailing list for annual distribution of Bibliography of Collaborative Perinatal Project Publications.

Literature searches upon request for specific article, subject, or author.

Coordination and Compilation of Annual Report in proper format for submission to NINDS Director.

II. PROBLEMS

Lack of personnel has resulted in a slowdown of operations. Backlogs exist in the following areas:

Subject indexing of reprints in our Reprint Retrieval File
Cutting, annotating and filing of reprints
Collection of reprints from Collaborating Institutions to update file

Priority has been given to individual needs of investigators for reference searches for ongoing studies with potential publication.

Definite forseen temporary loss of personnel for three months (maternity leave) will accentuate this problem. The need for a temporary replacement for this period is acute.

In addition, a permanent full-time clerk-typist is needed for the current operation and to reduce the accumulated backlog.

III. PROPOSED FUTURE OBJECTIVES

To eliminate backlog, disseminate information regarding our Collaborative Project and its publications to interested persons in the scientific and lay community.

With more and more Project data becoming available, it is anticipated that more studies will be generated and a heavier demand upon the Section for services and searches can be expected.

I. SECTION ON SPEECH, LANGUAGE AND HEARING
Report for the Period July 1, 1968 through June 30, 1969

I. SUMMARY OF ACTIVITIES AND DEVELOPMENTS

A. Routine

1. Processing of 3-year SLH forms. Status: near completion.
2. Accumulation of 8-year SLH forms. Status: continuing; early.
3. Supervision of inter-institutional quality control. Status: continuing.
4. Site visits by Section Head as Project Officer. Status: continuing.

B. New

1. Addition of Speech Pathologist to staff (August 1968).
2. Revision of 8-year forms and manual. Status: near completion.
3. Definition of codes for 8-year exam. Status: near completion.
4. Design of Language Organization scales. Status: complete.
5. Pretest of Language Organization scales. Status: continuing.
6. Addition of Boston as SLH collaborator. Status: beginning.
7. Study of parental attitudes and stuttering (with Dr. Raymond Holden). Status: continuing.

C. Discontinued

1. Development of 8-year summary form. Reason: significant inter-institutional differences in scores obviate its feasibility and utility.
2. Development of communicative index. Reason: ingredient subtests in 8-year battery do not sample communicative functions with sufficient range and depth for such a purpose.

D. Non-Project

1. Participation by Section Head as member of Surgeon General's study group dealing with the effects of sonic boom.
2. Address by Section Head on government programs to National Hearing Aid Society in Chicago, November 2, 1968.
3. Attendance at workshop by Section Head on Correlation of Temporal Bone Histopathology and Auditory Function, March 30 - April 4, 1969.

II. PROBLEMS

A. Personnel needs

1. Language Specialist (Speech Pathology).
2. Statistical assistant.
3. Secretary.

III. OBJECTIVES

A. Administrative

1. Promote data analyses and studies by collaborators.
2. Conduct SLH workshop on 8-year exam revisions and Language Organization scales.
3. Initiate use of Language Organization scales.
4. Establish criteria for executing SLH section of IDC-77.

B. Study

1. Analysis of 3-year data to determine whether institutional differences in reporting are due to population differences.
2. Same as item 1 for 8-year data.
3. Predictive value of selected behavioral variables at age 8 months, 3 year, 4 year and 7 year relative to communicative status at age 8 years.

Serial No. NDS (CF)-57 PR/ID 402
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Serological and Virus Isolation Studies of Infectious Diseases in the Collaborative Study on Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood.

Previous Serial Number: Same

Principal Investigators: Dr. John L. Sever, PRB, NINDS
Dr. David A. Fuccillo, PRB, NINDS
Mrs. Anita Ley, PRB, NINDS
Mrs. Renee Traub, PRB, NINDS
Mrs. Mary Ruth Gilkeson, PRB, NINDS

Other Investigators: Dr. Gabriel Castellano, MBA
Dr. Janet Hardy, Baltimore, Maryland
Dr. Sheldon Korones, Memphis, Tenn.

Cooperating Units: Collaborative Institutions in the Perinatal Research Study
Laboratory of Infectious Diseases, NIAID
NICHD
Cooperating Institutions in California and Hawaii (with the Section on Infectious Diseases)
Microbiological Associates

Man Years:

Total:	14.5
Professional:	5.5
Other:	9

Project Description:

Objectives: The purpose of the infectious disease investigations in the Perinatal Research Study is to determine insofar as possible the role of infections in the production of abnormal pregnancy outcomes. To accomplish this, serial specimens are taken throughout pregnancy, at delivery, and at six weeks postpartum. These sera are being tested with antigens to determine the antibody responses of the patients during pregnancy and postpartum, and then to relate this serological information to the clinical data for the pregnancy and the child. In addition, serum specimens from the children at one year of age were obtained from the last 10,000 study pregnancies and

these are now being studied. In special cases when congenital infection was suspected on the basis of clinical or laboratory findings, throat swabs and blood specimens were obtained from the children.

Methods Employed: To accomplish this program, blood specimens were obtained from pregnant women at set intervals throughout pregnancy and postpartum. Initially, during 1959 the collection of blood specimens was made once every trimester. Late in 1960 the requirements for the collection were increased and strengthened so that blood specimens were taken at the time of registration, at set intervals of approximately every two months throughout pregnancy, at delivery, and at six weeks postpartum. At the same time, a uniform method for the collection and processing was adapted as a required study procedure. The use of special Vacutainers, sterile technique, special sterile vials, and new shipping containers were all required. Intensive laboratory training sessions were held at NIH by the Section on Infectious Diseases for all technicians in the collaborating institutions. These sessions were repeated each year and a training film was prepared and sent to collaborating groups on request. Careful, complete control was maintained on all collection and processing of serum. At the Serum Center of the Section, personnel checked every vial of serum as received for quality and quantity. Regular reports of this information were sent every three months to each study institution. Telephone calls were made immediately to Project Directors whenever there was a decrease in the quality and quantity of sera received. Completeness of sets of specimens from each patient was also reviewed by Serum Center personnel. To improve the collection of complete sets of sera a special reporting form was devised for the collaborating institutions and monitored by the Section.

By the spring of 1961 all institutions attained the minimum requirement of 90% satisfactory specimens for quality and quantity. Satisfactory quality was defined as straw colored sera with no hemolysis. Satisfactory quantity was a minimum of 4 vials, each with 3 ml of serum and proper labels. At each meeting of the Project Directors a report was given concerning the quality and quantity of specimens submitted by each institution. This detailed intensive review was conducted throughout the entire time of sampling of sera from the mothers and continues at present with specimens being received from children at one year of age, special study specimens, and sera from cooperating groups.

Completeness of sets of serial specimens was determined from the sera submitted to the Serum Center of the Section and the special reporting form sent to the Section. Data for the first 28,386 patients showed that there was at least one specimen submitted for 94.2% of the patients. The majority of the omitted specimens occurred during the first months of 1959. A computer analysis of specimen set completeness was prepared.

With the development of a firm base for obtaining the required specimens and tissues, the program embarked on a large commitment for the development of necessary antigens, new techniques, and the training of a competent

laboratory staff for the study of the specimens. Antigen development was conducted by the personnel of the Section and experienced investigators under contract. Professional laboratory personnel were selected for the Section's Units on Statistics and Design, Serology, Virology, Experimental Animal Research, Immunological Studies, Epidemiology, and Experimental Pathology and Neurology. Three years ago the Unit on Cytogenetics was added. This program is jointly sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Diseases and Stroke.

To document the occurrence of an infection, two approaches are available: 1) Isolation of the microorganism from the patient or 2) Detection of an antibody rise in serum specimens. Both approaches are being used in the present studies. Appropriate isolation procedures for virus, bacteria, and protozoa are being used with throat swab specimens from the children. This approach was not used for detecting infections in the mothers since it would have required obtaining throat swab and anal specimens at the time of each infection. When this was been tried in the past, it has been unsuccessful because the women are usually unable to come to a laboratory for the collection of specimens when they have minor illnesses. Furthermore, a great many of the infections under consideration frequently do not result in significant illness of the women. These subclinical infections go unnoticed and unrecognized. For these reasons, the serological approach was selected. By collecting serial serum specimens, antibody levels for various viruses and protozoa can be determined. The development of antibody to a microorganism in a patient who was previously antibody negative provides indirect evidence for infection. The presence of specific antibody indicates prior exposure to that antigen or microorganism.

The serological test most frequently employed in these studies is the complement fixation method. This basic method has been used for many years as the Wasserman test for the diagnosis of syphilis. With the use of viral antigens the test is very versatile, performed rapidly, and provides broad coverage of a great many of the more than 125 viruses which are known to be of importance to man. Antigens were prepared for most of these viruses. Tests of specificity were conducted with animal sera. For man, considerable data is available from our studies and those of many other laboratories to indicate that both group and specific reactions occur with these antigens. The adenovirus CF (Type 2) antigen, for example, is group reactive and provides evidence for adenovirus infections in general. To date, there are 31 adenoviruses recognized for man. Rubella CF antigen on the other hand is very specific and detects infection with rubella only. The sensitivity, specificity, and persistence of the test is also known. With this type of information, it is possible to design serological studies for the viruses and protozoa. Bacterial antigens are usually not available for specific serological tests. Only direct evidence for these infections can be used. The history of infection as reported by the patient has proven to be quite unreliable in most cases and is only used as general information.

The majority of initial serological studies are conducted with the use of the complement fixation method. All tests are reproduced completely and a minimum of 90% agreement within twofold variation is required. All sera showing significant change in antibody, together with any sera which did not reproduce, are tested a third time. For more specific testing or confirmation of these results the hemagglutination inhibition and neutralization methods can be used. These latter serological procedures are very specific and are also employed for follow-up testing whenever the initial studies with the complement fixation method suggest the need for further investigation.

Major Findings: A total of 130 complement fixing antigens have been developed. Approximately three-fourths of the antigens have been thoroughly evaluated and are now being applied in routine testing of study sera. The development and maintenance of large quantities (1,000 ml) of satisfactory antigens for 45 viruses is an integral part of the investigation being carried on by the study. The other antigens are receiving intensive developmental work and 20 of these antigens are under test for specificity. Specific control antisera have been prepared for 85 microorganisms. In addition, to provide improved safety, extensive work has been conducted on the inactivation of the live virus antigens.

The serological studies are being conducted in accordance with three major study designs: First is the epidemiological studies to determine the frequency of virus experience among study populations. Specimens from representative patients at study hospitals are being tested for evidence of antibody. By studying these specimens, it is possible to establish the frequency of antibody and change in antibody titer to each virus. The data for each hospital is then analyzed in relation to other information from the Collaborative Perinatal Study, and in relation to other information from epidemiological data concerning the seasonal occurrence of abnormal pregnancies and children.

The second and most active category of study involves the selection of particular microorganisms for intensive testing. Studies of this type have involved, for example, the testing of sera from a large number of patients for antibody to toxoplasmosis or rubella. Intensive studies are now being conducted utilizing antigens for influenza A, mumps, cytomegalovirus, herpes simplex and rubella. Patients identified as having serological evidence for an infection are then grouped and clinical data for these groups and the remaining patients and their children are compared and analyzed.

Third, studies are designed to obtain maximum data concerning the virus experience of patients with abnormal pregnancy outcomes, and "matched control. The results of this type of study are then analyzed in terms of differences in frequency of antibody and antibody change among the abnormals and matched controls. The matching of the patients include factors which are known to influence virus experience, such as time of the year during which the specimens were obtained, race, age, number of living children in the family, and geographic location of the patients. These studies are conducted when a sufficient number

of abnormals of a particular type have been identified so that statistical analysis might establish valid information. The initial studies were directed at abnormalities which are relatively frequent, such as abortions, stillbirths, and neonatal deaths. The less frequent abnormalities or those which cannot be recognized in infancy or early childhood are being studied as greater numbers of these patients are identified in the Collaborative Study population.

Collaborating Studies: The primary deficiency of data in the Study has long been recognized as the late registration of Study patients. Since only 20% of the patients register during the first trimester of pregnancy, it is impossible to document adequately the infectious diseases experience of patients during the first trimester. To provide data on the first trimester of pregnancy, two additional Collaborative Studies were joined with the program of the Section on Infectious Diseases. These are:

1. Study of Viral Infections in Pregnancy
   Dr. Margaret Jones, UCLA and Kaiser Hospital in Los Angeles, Calif.

2. Study of Infections in the First Three Months of Pregnancy
   Dr. Robert McCallum, Kaiser Hospital, Honolulu, Hawaii

In addition to these studies, the collaboration with the Perinatal Study in the Kaiser Hospital in Oakland with Dr. Yerushalmy has been an integral part of the program since its initiation in 1959.

Significance to the Program of the Institute: The use of micro-serological techniques for a large group of new viruses provides an opportunity to investigate the course of human disease caused by viruses which are either difficult to isolate or are resistant to evaluation because the clinical effects are delayed until a long time after infection has subsided. This is particularly true in the case of birth defects. The application of this tool of analysis is providing valuable information on the epidemiological aspects of virus infections.

Proposed Course of the Project: The serological program will continue to be expanded in terms of antigenic materials and the collection of sera. New study arrangements for investigation of viral and genetic abortions have been developed with collaborating groups.

As additional abnormal pregnancy outcomes are reported, these will be added to existing studies on abortions, stillbirths, neonatal deaths, congenital malformations and mongols.

The initial "leads" obtained by the present serological testing are being explored in detail with the use of expanded serological investigations as well as other techniques of virology. It is clear that supplemental sampling is necessary for patients who register early in the first trimester of pregnancy and for those who have had repeated abnormal pregnancies. Arrangements have been developed for obtaining full sets of serum specimens and data for patients

who abort or have stillbirths. Specimen collection for the virus studies has been expanded to include tissue samples from abortuses, stillbirths, and neonatal deaths so that direct isolation of viral agents is included and extends the serological findings.

Honors and Awards: None

Publications:

Hancock, M. P., Huntley, C. C., and Sever, J. L.: Congenital rubella syndrome with immunoglobulin disorder. J. Ped. 72: 636-645, 1968.

Katz, R. G., White, L. R., and Sever, J. L.: Maternal and congenital rubella. Clin. Ped. 7: 323-330, 1968.

Resnick, J. S., Engel, W. K., and Sever, J. L.: Subacute sclerosing panencephalitis. Spontaneous improvement in a patient with elevated measles antibody in blood and spinal fluid. New Eng. J. Med. 279: 126-129, 1968

Hildebrandt, R. J., Sever, J. L., and Anderson, B.: Preservation of infectious cytomegalovirus. Proc. Soc. Exper. Biol. & Med. 129: 504-506, 1968.

Ueda, K., Takabayashi, K., Nunoue, T., Nishio, S., Kimoto, K., Nagayama, T., and Sever, J. L.: Frequency of rubella antibody among children in Fukuoka in Southern Japan. Fukuoka Acta Medica 59: 784-786, 1968.

Jabbour, J. T., and Sever, J. L.: Serum measles antibody titers in patients with SSPE, compared with parents and siblings. J. Ped. 73: 905-907, 1968.

Sever, J. L.: Recurrent rubella - reality or rumor? JAMA 206: 2749-2750, 1968.

McCracken, G. H. Jr., Chen, T. C., Hardy, J. B., and Tzan, N.: Serum immunoglobulin levels in newborn infants: I. Evaluation of a radial diffusion plate method. J. Ped. 74: 378-382, 1969.

McCracken, G. H. Jr., Hardy, J., Chen, T. C., Hoffman, L. S., Gilkeson, M. R. and Sever, J. L.: Serum immunoglobulin levels in newborn infants: II. Survey of cord and follow-up sera from 123 infants with congenital rubella. J. Ped. 74: 383-392, 1969.

Serial No. NDS (CF)-61 PR/ID 835
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Clinical Investigations in Human Volunteers and Other Populations of Virus Effects and Production of Prototype Human Antisera and Vaccines

Previous Serial Number: Same

Principal Investigators: Dr. John L. Sever, PRB, NINDS
Dr. Stephen J. Newman, PRB, NINDS

Other Investigators: Dr. David A. Fuccillo, PRB, NINDS

Cooperating Units: Bureau of Prisons, Department of Justice
(Dr. Myrl Alexander, Director)
Petersburg Federal Reformatory
(Dr. Paul Levitt, Chief Medical Officer)

Man Years:

Total:	1
Professional:	1/2
Other:	1/2

Project Description:

Objectives: To study the efficacy of prophylactic and therapeutic materials for the prevention and control of infectious diseases. To study the safety, antigenicity, communicability and immunogenicity of candidate rubella vaccines.

Methods Employed: Human volunteer studies are conducted in collaboration with the Federal Bureau of Prisons. These studies are reviewed and approved by the Clinical Research Committee and the Medical Board of the National Institutes of Health, and the Vaccine Development Board of the National Institute of Allergy and Infectious Diseases.

Major Findings: Volunteer studies were performed to evaluate the safety, immunogenicity and communicability of HPV-77/WI 6 live attenuated rubella vaccine. The vaccine was ineffective in inducing immunity and there was no spread of virus.

Significance to the Program of the Institute: Volunteer studies provide the basic data necessary to evaluate potential rubella vaccines. These

studies provide important and necessary information on the effectiveness and safety of such preparations.

Proposed Course of the Project: Additional studies will be performed when necessary or appropriate.

Honors and Awards: None

Publications:

White, L. R., Leikin, S., Villavicencio, O., Abernathy, W., Avery, G., and Sever, J. L.: Immune competence in congenital rubella: Lymphocyte transformation, delayed hypersensitivity, and response to vaccination. J. Ped. 73: 229-234, 1968.

Serial No. NDS (CF)-62 PR/ID 972
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Experimental Animal Tissue Culture, Histopathological and Serological Investigations of the Role of Viruses and Other Microorganisms in the Perinatal Period.

Previous Serial Number: Same and incorporating Serial Nos. NDS (CF)-67 PR/ID 1504 and 1505.

Principal Investigators: Dr. William T. London, PRB, NINDS
Dr. David A. Fuccillo, PRB, NINDS
Dr. John L. Sever, PRB, NINDS

Other Investigators: Mrs. Anita C. Ley, PRB, NINDS
Miss Blanche Anderson, PRB, NINDS
Miss Ruthann Kibler, PRB, NINDS

Cooperating Units: None

Man Years:

Total:	3-1/2
Professional:	2
Other:	1-1/2

Project Description:

Objectives: The infection of gravid and non-gravid animals of several different species by oral and all parenteral routes with various viruses and other microorganisms to determine the effects of these agents on the animals and their fetal tissues.

Attempt to recover inoculated agents from the various animals and fetal tissues and the correlation of these reisolations with time (in gestation) of inoculation, route of inoculation, and dosage given.

Correlate these findings with gross and histopathological findings.

Correlate all of this information with serological findings.

Methods Employed: An investigation of the role of viruses and other microorganisms in the perinatal period by the continual use of experimental animals; tissue culture techniques; histopathological studies; and serological testing.

Pregnant and non-pregnant animals of various species including monkeys are being inoculated by various routes with viruses and other microorganisms. These animals are being observed and checked for evidence of disease and/or effects on fetal tissues.

Virus isolation investigations utilizing tissue culture to recover viruses from tissues and fluorescent antibody technique to study the location of virus infection produced in experimental animals.

Histopathological and gross anatomical studies (Alizarin red technique) are conducted on specimens obtained from the experimental animal studies.

Extensive serological studies are conducted with the many viral antigens developed for the Collaborative Study and new antigens with materials being studied previously mentioned.

Major Findings: Animal investigations with pregnant rabbits inoculated intravenously with tissue culture grown rubella virus early in pregnancy produced "runting" in the offspring. Neutralizing and HI antibodies developed in all inoculated animals. Virus was recovered from infected animals 7-11th day postinoculation. Virus was isolated from fetal tissue taken on the 29th day of gestation and at time of birth. Staining of fetuses with Alizarin red has demonstrated retarded bone development in the carpal and tarsal bones of infected fetuses when compared with controls.

High passage rubella virus (HPV-77) did not affect fetal growth in pregnant monkeys. High titers of HI antibodies were produced in inoculated animals, however, the virus was not isolated from the products of conception.

Inoculations of pregnant monkeys with tissue culture grown monkey cytomegalovirus early in pregnancy have not demonstrated interference with gestation.

Neutralizing antibodies developed in inoculated animals. Virus was recovered from the urine of inoculated animals.

Significance to the Program of the Institute: A program using experimental animals, tissue culture techniques, and histopathological investigations complements the strict serological approach being used on human sera obtained from the Collaborative Study and thus balances the investigations of the role of viruses and other microorganisms in the perinatal period. It presents the direct means of investigation of these agents which may contribute to perinatal pathology.

Proposed Course of the Project: Further studies of experimental cytomegalic inclusion virus in pregnant and non-pregnant monkeys are in progress. Teratogenic studies have been started with herpes simplex, influenza (Hong Kong strain) and toxoplasmosis. These agents have been injected into pregnant monkeys and studies are being carried out.

Honors and Awards: None

Publications:

Sever, J. L., and London, W. T.: Viruses and embryos. Teratology 2: 39-45, 1969.

London, W. T., Fuccillo, D. A., and Sever, J. L.: Congenital rubella in rabbits. International Symposium on Rubella Vaccines, London, 1968; Symp. Series Immunobiol. Standard. 11: 121-124, Basel/New York, S. Karger, 1969.

Rorke, L. B., Fabiyi, A., Elizan, T. S. and Sever, J. L.: Experimental cerebrovascular lesions in congenital and neonatal rubella-virus infections of ferrets. Lancet, pp. 153-154, 1968.

Serial No. NDS (CF)-65 PR/ID 1238
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Chromosomal Studies and Isolation of Infectious Agents from Tissues

During FY 1969 this project was incorporated into Serial No. NDS (CF)-69 PR/ID 1732

Serial No. NDS (CF)-65 PR/ID 1270
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Toxoplasmosis: Serological and Clinical Studies.

Previous Serial Number: Same

Principal Investigator: Dr. John L. Sever, PRB, NINDS

Other Investigators: Dr. Joseph S. Drage, PRB, NINDS

Cooperating Units: Section on Pediatric Neurology, PRB, NINDS

Man Years:

Total:	.4
Professional:	.2
Other:	.2

Project Description:

Objectives: This study relates rises in antibody titer to abnormal pregnancy outcomes.

Methods Employed: Within the Pediatric Neurology Section, a hand review was completed on 128 cases that had shown various degrees of titer rise.

Major Findings: Within the group of 47 patients with titer elevations of greater than 4096, or significant increases in antibody titer, five were found to have definite toxoplasmosis and ten were suspected of having toxoplasmosis. The ten included six with motor retardation, two pregnancies resulting in stillbirths and two in neonatal deaths. The sera from ten of the remaining 37 apparently normal children were tested for antibody to toxoplasmosis and one was found to have a high titer.

Proposed Course of the Project: Study in progress awaiting computer analysis.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-66 PR/ID 1326
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Rubella Vaccine Development Program

During FY 1969 this project was incorporated with Serial No. NDS (CF)-61 PR/ID 835.

Serial No. NDS (CF)-67 PR/ID 1502
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Immunological Studies of Virus Infections in Experimental Animals and Man

During FY 1969 this project was incorporated with Serial No. NDS (CF)-69 PR/ID 1731.

Serial No. NDS (CF)-67 PR/ID 1503
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Epidemiologic Studies of Perinatal Infections

Previous Serial Number: Same

Principal Investigators: Dr. John L. Sever, PRB, NINDS
Mrs. Dorothy M. Yarnick, R.N., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	1-1/2
Professional:	1-1/2
Other:	0

Project Description:

Objectives: To utilize information from the Collaborative Perinatal Research Study and other cooperative studies to identify pregnancies complicated by maternal infections or infections in childhood; to further delineate these cases by serologic testing of the stored sera; to utilize Collaborative Study and related data to determine outcome of these pregnancies in relation to the outcomes of matched controls and the general study population in order to gain information on the frequency of maternal infections during pregnancy and their effects on the developing fetus. Studies include: Bronchodilators-Asthma Study VII 1; Inguinal Hernia - Infection and Associated Malformations VII 2; Toxoplasmosis and Parasitic Infections VII 3; Syphilis - Toxoplasmosis Study VII 4; Unknown Infections - Toxoplasmosis Study VII 5; Herpes Simplex VII 6; Rubella VII 7; Neoplastic Diseases and/or other Tumors VII 8; Grade III - Pap Smears VII 9.

Methods Employed: Primary material utilized for these studies comes from the Perinatal Research Study and other cooperative studies. For this reason the serologic data developed by the Section on Infectious Diseases is correlated with the clinical information available either from print-outs or direct hand review of the charts stored in the Perinatal Research Branch.

Major Findings: These studies have shown a correlation between inguinal hernias and maternal rubella in the first trimester of pregnancy. Investigations have failed to show any relation between these bronchodilators and

abnormal fetal outcome. The investigation of toxoplasmosis in relation to parasitic infections has suggested a high rate of toxoplasmosis among women who have experienced parasitic infections of certain types. This is being extended in studies in Puerto Rico. The data for rubella has documented the association of rubella in the second trimester as causing fetal damage in approximately 10% of the pregnancies. Further studies are now in progress on the relation of neoplastic diseases with herpes simplex.

Significance to the Program of the Institute: The development of the serologic data requires the further analysis in relation to the epidemiology of infections in the Perinatal Research Study as well as the epidemiology of perinatal infections with other collaborating groups. This data then provides the basis for correlating serologic and clinical information. Special studies are initiated in populations where high frequencies of infection or abnormal pregnancy outcomes have been noted.

Proposed Course of the Project: Special emphasis will be placed on the possible association of neoplastic diseases and other tumors with herpes simplex infections and further identification of the factors involved in the transmission of toxoplasmosis. In addition, we will extend our epidemiologic information on subacute sclerosing panencephalitis and other diseases of the central nervous system which appear to have unusual foci of infection and throughout the country.

Honors and Awards: None

Publications:

Hardy, J. B., McCracken, G. H., Jr., Gilkeson, M. R., and Sever, J. L.: Adverse fetal outcome following maternal rubella after the first trimester of pregnancy. JAMA 207: 2414-2420, 1969.

Serial No. NDS (CF)-67 PR/ID 1504
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Experimental Pathology and Neurology of Infections of the Central Nervous System
A. Fluorescent antibody studies on rubella-infected newborn ferrets

During FY 1969 this project was incorporated with Serial No. NDS (CF)-62 PR/ID 972

Serial No. NDS (CF)-67 PR/ID 1505
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Experimental Pathology and Neurology of Infection of the Central Nervous System
B. The pathogenesis of mouse cytomegalovirus infection by fluorescent antibody technique

During FY 1969 this project was incorporated with Serial No. NDS (CF)-62 PR/ID 972.

Serial No. NDS (CF)-67 PR/ID 1506
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Maternal Infection and Pregnancy Outcome

Previous Serial Number: Same

Principal Investigators: Dr. David A. Fuccillo, PRB, NINDS
Dr. John L. Sever, PRB, NINDS
Dr. Robert J. Huebner, NIAID

Other Investigators: Dr. William T. London, PRB, NINDS
Mrs. Renee Traub, PRB, NINDS
Mrs. Mary Ruth Gilkeson, PRB, NINDS
Mrs. Flora Moder, PRB, NINDS

Cooperating Units: Laboratory of Infectious Diseases, NIAID
University of California (Dr. Margaret H. Jones)
Hawaii Permanente Medical Group (Dr. Paul F. McCallin)
University of Puerto Rico, School of Tropical Medicine
(Dr. Dolores Mendez-Cashion)

Man Years:

Total:	4.5
Professional:	1.0
Other:	3.5

Project Description:

Objectives: To utilize various virological techniques in an intensive study of viruses to determine their role in the production of birth defects and related abnormalities. To develop virological techniques necessary for the investigation of the natural course of the disease as caused by the infectious agents.

Methods Employed: The standard virus isolation in serum neutralization tests was used for large scale testing in the study of pregnant women and their children. The development of new techniques, such as the HI test and the use of the RK_1 direct CPE neutralization test, helps determine the frequency of virus experience among study populations along with the presence of antibody and change in antibody titer to the virus. The RK_1 neutralization test is being used to establish the reliability of the HI test and determine its sensitivity and specificity. A serologic study utilizing these tests on sera collected on the collaborative population during 1966 was conducted to

determine the current susceptibility of pregnant women to rubella. During and following the epidemic of 1964 specimens of the placenta were obtained from a majority of the deliveries. Utilizing this placental material, we are completing the testing of 1500 placentas of rubella virus for the purpose of identifying children with congenital rubella by the presence of rubella in the placenta material. Many of the defects caused by maternal infections are not obvious in the very young infant and in fact may be seen in the process of developing in the postnatal period. The use of a latex anti-IgM test may prove to be a valuable method to screen for high IgM levels.

Major Findings: Serum specimens were obtained from 500 pregnant women registered during January through April 1966. It was found that there was a significant reduction in the frequency of pregnant women without antibody. There were 7.8% found to be susceptible as compared to 17.5% in 1962. At the present time there are more white susceptible patients (10%) than Negro (3.9%). The high susceptibility is no longer highest among the young patients but among women 16 years or over. It would appear that approximately 8% of the pregnant women in this population remain susceptible to rubella. Other studies are directed towards investigation of the prevalence of virus experience in the population under surveillance, also specific studies of infection among patients whose pregnancy terminated in an abnormal outcome are being conducted. Recent studies indicated that there is approximately 10% possibility of an abnormal fetus being produced after rubella infection in the second trimester. Special studies are being directed toward abnormal pregnancy outcome which can be recognized shortly after birth, such as abortions, stillbirths, neonatal deaths, and congenital malformations including congenital heart defects. Several viruses have been found to occur in high frequency in specific patients with abnormal pregnancy outcomes. Particular emphasis in the studies relate Coxsackie B virus. Other viruses which are of interest include cytomegalovirus and herpes virus.

Neutralization results with RK_1 cultures indicate the neutralization test is somewhat more sensitive in detecting long term antibody to rubella.

Significance to the Program of the Institute: The results from these studies will help determine what effect virus infection has on abnormal pregnancy outcomes and will also provide valuable information on the epidemiological aspects of virus infections.

Proposed Course of the Project: New study arrangements for investigation of viral infections and their possible effect on the genetic mechanisms and immunological competence are being developed. Other studies will be conducted in cooperation with the several collaborating groups concerning the role of viruses in the etiology of abnormal children.

Honors and Awards: None

Publications:

Gitnick, G. L., Fuccillo, D. A., Sever, J. L. and Huebner, R. J.: Progress in rubella vaccine development: Review and studies of growth of rubella in chick embryo tissue culture. Am. J. Pub. Hlth. 58: 1237-1247, 1968.

Whitmore, C. E., Fuccillo, D. A., Gitnick, G. L., and Sever, J. L.: Problems in the detection of rubella virus in African green monkey kidney tissue culture. Proc. Soc. Exper. Biol. & Med. 128: 253-257, 1968.

Sever, J. L., Fuccillo, D. A., Gilkeson, M. R., Ley, A., and Traub, R.: Changing susceptibility to rubella. Ob. & Gyn. 32: 365-369, 1968.

Fuccillo, D. A., Sever, J. L., Gitnick, G. L., Traub, R. G. and Huebner, R. J.: Rubella neutralizing antibody determinations with the rabbit kidney cell strain LLC-RK_1. Proc. Soc. Exper. Biol. & Med. 129: 650-652, 1968.

Sever, J. L., Shanbrom, E., Steinmeier, R., Schacher, S. A., McCracken, G., and Fuccillo, D. A.: Latex reagent for determining IgM levels in cord and newborn sera. J. Immuno. 102: 679-681, 1969.

Fuccillo, D. A., Sever, J. L., Gitnick, G. L., and Traub, R.: Disagreements in antibody determinations. International Symposium on Rubella Vaccine, London, 1968; Symp. Series Immunobiol. Standard. 11: 211-214, Basel/New York, S. Karger, 1969.

Gitnick, G. L.: An improved diluent for rubella hemagglutination and HI tests. Appl. Microbiol. 16: 691-694, 1968.

Serial No. NDS (CF)-69 PR/ID 1729
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Study of the Possible Transmission of Toxoplasmosis in Humans via Intestinal Parasites

Previous Serial Number: None

Principal Investigators: Dr. John L. Sever, PRB, NINDS
Dr. Stephen J. Newman, PRB, NINDS
Dr. David A. Fuccillo, PRB, NINDS
Dr. Dolores Mendez-Cashion, Puerto Rico

Other Investigators: None

Cooperating Units: Department of Pediatrics
Centro-Medico
San Juan, Puerto Rico

Man Years:

Total:	1/2
Professional:	1/4
Other:	1/4

Project Description:

Objectives: To determine the mode of transmission in human toxoplasmosis.

Methods Employed: Puerto Rican children were studied for antibodies to toxoplasmosis and for intestinal parasites.

Major Findings: Study is in progress.

Significance to the Program of the Institute: Although much is known about toxoplasmosis as a disease, little is known about the mode of transmission. This study may shed some light on this aspect of the disease.

Proposed Course of the Project: Completion of toxoplasmosis project.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/ID 1730
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Various Studies of the H-1 and RV Viruses

Previous Serial Number: None

Principal Investigators: Dr. John L. Sever, PRB, NINDS
Dr. Stephen J. Newman, PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total: 1/2
Professional: 1/4
Other: 1/4

Project Description:

Objectives: To further determine the importance of the H-1 and RV viruses in human disease states.

Methods Employed: Sera from selected patients (abortions) are studied for antibodies to H-1 and RV viruses.

Major Findings: Study in progress.

Significance to the Program of the Institute: The studies of H-1 and RV viruses should add to the small fund of information about these viruses.

Proposed Course of the Project: Completion of H-1 and RV studies.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/ID 1731
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Study of the Role of Interferon in Chronic Infection. Relationship between Interferon Producing Capacity and Virulence of Herpes Simplex Virus Strains. Studies of Diseases of the Central Nervous System Suspected to be Associated with Latent Viruses. Experimental Tissue Culture Techniques for Virus Isolations. Development of Immunologic Methodology.

Previous Serial Number: Formerly NDB (CF)-67 PR/ID 1502

Principal Investigators: Dr. Luiz Horta-Barbosa, PRB, NINDS
Dr. David A. Fuccillo, PRB, NINDS
Dr. L. Catalano, NICHD
Dr. William T. London, PRB, NINDS
Dr. John L. Sever, PRB, NINDS

Other Investigators: Mrs. Anita Ley, PRB, NINDS
Mrs. Barbara Wittig, PRB, NINDS
Mrs. Rebecca Hamilton, NICHD

Cooperating Units: Indiana University Medical Center (Dr. Wolfgang Zeman)
University of Tennessee (Dr. J. T. Jabbour)

Man Years:

Total:	4
Professional:	2
Other:	2

Project Description:

Objectives: To determine whether peripheral white cells, serum, and spinal fluid from patients with subacute sclerosing panencephalitis (SSPE) are capable of reacting against explants of mouse and human cerebellum in vitro producing the demyelination and cyto-destruction observed in vivo. These experiments are designed to study the possible role of a mediated delayed hypersensitivity and/or the contribution of antibody to the brain lesions.

Cultures of SSPE brain biopsies, lymphatic organs, and buffy-coat from patients are used in attempts to reproduce the disease experimentally as well as to isolate an infectious agent.

Cerebrospinal fluid and serum samples from SSPE patients are assayed for circulating interferon and peripheral leukocytic response to interferon inducers evaluated to establish whether the non-immune defense mechanisms are deficient.

The pathogenic properties of herpes simplex virus (Type I, and Type II) may be directly proportional to the amount of interferon induced by each type during the course of infection. To demonstrate this correlation in vitro studies with HSV are conducted in parallel with mice inoculation experiments.

Attempts to develop a new serologic technique using precipitation of radiolabeled rubella virus with specific antibody and antiglobulin. This should be a highly sensitive and specific serologic test.

Methods Employed: SSPE brain homogenates and dispersed cells obtained by trypsinization were used to inoculate laboratory animals and tissue culture systems. SSPE brain cells grown in tissue cultures were used to prepare "mixed cultures" by combining the brain astrocytes with stable cell lines in such a manner that the final "co-culture" would yield about 6 foreign cells for each astrocyte.

Whenever available, tonsils, adenoids, and other lymphatic organs from SSPE patients were included in tissue culture studies and utilized as potential virus sources. Peripheral leukocytes were also included in virus isolation studies.

Explants of 24-hour mouse cerebellum and human cortex obtained from therapeutic abortions were prepared by the method described by Bourstein and Murray. Only the explant cultures showing myelin formation were included in studies using serum, spinal fluid and leukocytes from SSPE patients.

Interferon levels in serum and spinal fluid of SSPE patients were obtained by the plaque inhibition method using Vesicular Stomatitis Virus as the challenge virus. Patient's white cells were grown in vitro, infected with different viruses (including measles), and interferon on supernatants measured by the plaque inhibition method.

The pathogenesis of herpes simplex virus, types I and II, was studied in mice and viral and non-viral interferon inducers were used in attempts to block HSV encephalitis. Mouse L-cell monolayers were used to evaluate interferon response induced by the two HSV strains and to correlate interferon inducing capacity of each strain with plaque size produced under agar overlay.

The Gilchrist strain rubella virus was used in attempts to prepare tritium labeled purified virus. The final goal of this work is to develop a radioisotope precipitation test for rubella. A similar test has been used to increase the sensitivity and scope of serologic tests involving bacterial and rickettsial antigens. Preparation of radioactive rubella virus in tissue culture represents no problem, but the purification of the virus involves

rather complicated biochemical methods.

Major Findings: The atypical virual infection observed in children with SSPE was demonstrated to be caused by a suppressed measles virus. With the mixed brain cell culture developed in this laboratory it was possible to rescue the measles virus genome and to release complete infectious virus. The isolation of fully transmissible rubeola virus was accomplished only when the mixed culture technique with HeLa cells was utilized. Extensive tissue culture and serologic studies with the SSPE virus isolated from two brain biopsies indicate that the agent is antigenically similar to other strains of measles, but it is extremely well adapted to a wide spectrum of tissues, producing high titers when compared to the other strains.

Interferon was not present in serum nor in spinal fluid specimens from SSPE patients. However, leukocytes from these individuals responded as well as normal leukocytes to viral interferon inducers.

Poly I-C, a potent interferon inducer, was found to significantly protect mice against herpes virus encephalitis. Further studies are being carried out in vivo and in vitro.

Significance to the Program of the Institute: The development of a mixed brain cell culture technique to unmask latent infections of the central nervous system provides a new methodology for the study of chronic diseases of the CNS suspected to be related to viral etiologies. This approach should also be considered for non-neurological diseases which may be associated with abortive viral infections, such as polymyositis and systemic lupus erythematosus.

Proposed Course of the Project: Special emphasis will be placed upon a brain culture research program. Investigation of the mechanism of pathogenesis and possible immune deficiencies in patients with neurological diseases will be conducted. Our selection of patients with multiple sclerosis, Parkinson's disease, progressive multifocal leukoencephalopathy, and amyotrophic lateral sclerosis is supported by the existing data which suggest possible viral etiologies for each of these diseases. Tissue specimens and blood from patients will be provided through collaborative-contract arrangements with investigators throughout the country.

Utilizing the mixed culture technique we hope to determine if it is possible to release suppressed virus from these chronic neurologic diseases and to gain a further understanding of the pathogenesis of latent infections of the CNS. Antibody levels and competence of lymphocytes from patients will be examined using the standard techniques.

The SSPE strain of measles virus will be studied in laboratory animals and efforts will be directed at the development of an animal model system for this disease.

Honors and Awards: None

Publications:

Warren, J., Mason, R. J., Horta-Barbosa, L., Gabbard, K. L., and Bucy, M.: Increased susceptibility to murine hepatitis virus infection by treatment with iron salts. Proc. Soc. Exper. Biol. & Med. 129: 637-642, 1968.

Horta-Barbosa, L., Fuccillo, D. A., Sever, J. L., and Zeman, W.: Subacute sclerosing panencephalitis: Isolation of measles virus from a brain biopsy. Nature 221: 974, 1969.

Horta-Barbosa, L., Fuccillo, D. A., and Sever, J. L.: Rubella Virus. In Current Topics in Microbiology. Berlin, Springer-Verlag, Vol. 47, 1969.

Jabbour, J. T., Garcia, J. H., Lemmi, H., Ragland, J., Duenas, D. A., and Sever, J. L.: Subacute sclerosing panencephalitis. JAMA 207: 2248-2254, 1969.

Horta-Barbosa, L., Fuccillo, D. A., London, W. T., Jabbour, J. R., Zeman, W., and Sever, J. L.: Isolation of measles virus from brain cell cultures of two patients with subacute sclerosing panencephalitis. Proc. Soc. Exper. Biol. & Med. (In press).

Serial No. NDS (CF)-69 PR/ID 1732
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Investigation of the Role of Mycoplasma spp. and Other Microorganisms in the Perinatal Period.

Previous Serial Number: Formerly NDS (CF)-65 PR/ID 1238.

Principal Investigators: Dr. David L. Madden, NICH&HD
Dr. William T. London, PRB, NINDS
Dr. John L. Sever, PRB, NINDS

Other Investigators: Dr. Richard L. Horton, NIAID
Dr. Paul McCallin, Kaiser Permanente Medical Group, Honolulu, Hawaii
Mr. Kenneth Moats, PRB, NINDS

Cooperating Units: NICH&HD
Laboratory of Bacterial Immunology, NIAID
Kaiser Permanente Medical Group, Honolulu, Hawaii

Man Years:

Total:	2
Professional:	1
Other:	1

Project Description:

Objectives: To study the role of Mycoplasma spp. in perinatal diseases of man. To develop animal models for these mycoplasmal diseases in order to determine the pathogenesis of these diseases.

Methods Employed: Tissues obtained from aborted women are being received from the Kaiser Hospital, Honolulu, Hawaii. These specimens are being cultured in standard mediums for both classical and T-strain Mycoplasma. Serum samples obtained at time of abortion, 4-6 weeks later and from matched controls are being studied for the presence of Mycoplasma antibodies by the micro-metabolic-inhibition technique.

Vaginal and oral swabs and serum have been obtained from Grevit and rhesus monkeys. These specimens have been cultured in standard medium for classical Mycoplasma. Antibody in this serum will be determined by standard micro-metabolic-inhibition tests. This information will form the basis for trying to develop an animal model system in monkeys to study the effect of human

mycoplasmas recovered from perinatal diseases.

Three strains of Mycoplasma have been inoculated into a variety of animal hosts. M. arthritidis, isolated from man (M. hominis Type II) and from rats, was inoculated into germfree and conventional rats, monkeys and Gerbils. M. hominis, isolated from man, was inoculated into monkeys, and a Mycoplasma isolated from chickens was inoculated into germfree chickens. By use of standard isolation, serological and histopathological techniques the pathogenesis of these diseases will be studied.

Major Findings: From over 200 nonseptic abortions obtained over the past two years, mycoplasmas have been isolated from 10% of them. Most of these isolates have been classified as M. hominis. Preliminary serological studies on sera obtained from these patients and matched controls indicate that there is no significant difference in mycoplasmal titers.

It has been established that the normal flora of monkeys include M. salivarium and M. orale II. In addition, from the Grevit monkeys, the navel strain was occasionally isolated. Also, from the Grevit monkeys a serotype not in our collection was isolated. This may prove to be a new serotype. Significantly, M. orale I, the most commonly recovered serotype from man, was not recovered from these monkeys. Also, M. fermentans and M. pneumoniae were not isolated. M. hominis and M. laidlawii were occasionally isolated.

Preliminary studies in Grevit monkeys with M. hominis and M. arthritidi indicate that neither produce signs of disease nor serological response when given intravenously or intratracheally. When M. arthritidis in 0.5% agar was inoculated into the foot pad, antibody was detected, but no signs of disease were observed. In no case were organisms isolated from the blood or oral swab cultures 4 days postinoculation.

Significance to the Program of the Institute: A program devoted to studying the effect of Mycoplasma in perinatal infections complements the virological studies currently being done. This study and the support given to other investigators may more accurately define the role of Mycoplasma in disease.

Proposed Course of the Project: Further studies on the occurrence of Mycoplasma in non-septic human abortions are in progress. Attempts to define the association of Mycoplasma in normal deliveries are being made. Studies on the pathogenesis of Mycoplasma in monkeys will be continued to see if an animal model for septic and non-septic abortion and other perinatal infections can be developed.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/ID 1733
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Viral Diseases of the Nervous System

Previous Serial Number: None

Principal Investigator: Dr. L. W. Catalano, Jr., NICH&HD

Other Investigators: Dr. John L. Sever, PRB, NINDS
Dr. S. Baron, LVD, NIAID

Cooperating Units: Laboratory of Viral Diseases, NIAID
Georgetown University School of Medicine
(Dr. J. A. Bellanti)
Harvard Medical School (Dr. L. Johnson)

Man Years:

Total:	2
Professional:	1
Others:	1

Project Description:

Objectives: The main objectives of this project are: (1) to investigate the role of immune and non-immune (interferon) mechanisms in the pathogenesis of viral encephalitis; (2) to specifically investigate the role of herpes simplex virus in the causation of acute and chronic central nervous system disease in the adult and fetus; (3) to establish the clinical and biological significance of the two different strains of herpes simplex virus (Type I, "oral" and Type 2, "genital") in the causation of human disease.

Methods Employed: The principal methods employed are: (1) the quantal cross-microneutralization test, by which type-specific herpes virus antibody is identified; (2) the induction of interferon by polyinosinic-polycytidylic ribonucleic acid and investigation of the protection afforded by this material in experimental viral encephalitides; (3) mass serological surveys of selected patient materials with specific disease entities and during pregnancy; (4) virus isolation, titration and characterization procedures; (5) interferon titration via plaque reduction assays; and (6) experimental primate infection with herpes viruses, and to investigate the pathogenesis of such infection in the adult and fetus.

Major Findings: (1) Development of a reliable and highly versatile micro cell culture system for virological investigations; (2) demonstration that the artificial induction of interferon with polyinosinic-polycytidylic ribonucleic acid can afford protection against experimental herpes simplex virus and encephalomyocarditis virus encephalitis. (Presented at the American Federation Meetings, April 18, 1969); (3) evidence was obtained through a documented case study that herpes simplex encephalitis may occur by intrafamilial transmission of the virus.

Significance to Biomedical Research and the Program of the Institute: These investigations attempt to elucidate the pathogenesis of viral infections of the nervous system in the adult and fetus using immunological and virological techniques. Herpes simplex virus has been one agent which has received particular attention in these studies, since it has significant neurotropic capabilities in terms of newborn and adult encephalitides. There is considerable speculation that this virus may have latent, "slow" virus potential in relationship to chronic diseases of humans, including carcinoma and central nervous system infection. Continued investigation of the clinical and biological properties of the two strains of herpes simplex virus may permit more definitive establishment of such capabilities. Furthermore, the therapeutic potential of artificial interferon inducers as anti-viral agents needs to be further established and investigated, particularly in relationship to central nervous system infections.

Proposed Course of Project: (1) Type-specific quantile microneutralization serologic surveys of herpes simplex virus antibodies in a) pregnant women (and correlation with pregnancy outcome); b) patients with multiple sclerosis and amyotrophic lateral sclerosis; c) carcinoma of the cervix and other selected tumors; and d) experimentally infected pregnant and non-pregnant primates. (2) Continued investigation of the efficacy of polyinosinic-polycytidylic ribonucleic acid in experimental viral infections, including encephalitides. (3) Further studies on the biological (in vitro) and clinical differences between the two types of herpes simplex virus.

Honors and Awards: None

Publications:

Fuccillo, D. A., Catalano, L. W., Jr., Moder, F., Debus, D. A., and Sever, J. L.: Minicultures of mammalian cells in a new plastic plate. Appl. Micro. 17: 619-622, 1969.

Serial No. NDS (CF)-63 PR/OC 1144
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: An Instrument For The Conduct Of A Retrospective Study Of Seizures, Cerebral Palsy, Mental Retardation and Other Neurological and Sensory Disorders of Infancy and Childhood.

Previous Serial Number: Same

Principal Investigators: Z. A. Shakhashiri, M.D., PRB, NINDS
Leonard V. Phelps, PRB, NINDS
Glen S. Bartlett, M.D., PRB, NINDS

Other Investigators: Lenore Bajda, M.D., PRB, NINDS
John R. Day, M.D.
Blanche L. Vincent, S.N.O., PRB, NINDS
Zula C. Meekham, B.S.N., PRB, NINDS
Rose R. Tortorella, PRB, NINDS

Cooperating Units: Georgetown University Hospital, Retarded Children's Clinic, Selected Maternity Hospitals and Physicians in Metropolitan Washington

Man Years:

Total:	.35
Professional:	.30
Other:	.05

Project Description:

Objectives: Design an instrument for the conduct of a retrospective study of seizures, cerebral palsy, mental retardation and other neurological and sensory disorders of infancy and childhood in order to test certain basic and important hypotheses concerning the occurrence of neurological damage.

Methods employed: Recognized damaged outcomes of pregnancy, such as seizures, diplegias, hemiplegias and choreoathetoids are to be studied and related to defined perinatal or postnatal events. These outcomes were selected because they were construed to be related to or manifestations of or involved in the biological or psycho-sociological mechanism underlying the following hypotheses: (1) anoxia, (2) toxic influences on the brain, (3) metabolic influences, (4) trauma to the head, (5) infection of the brain, (6) dehydration of the child, (7) genetic or familial patterns, and (8) socioeconomic status.

Proposed Course of the Project: The abstraction of the maternity and nursery records and interviewing of the mothers have been completed. The physicians of sib controls have been contacted and information attesting to the health status of these sibs has been obtained. All forms have been edited and coded, and IBM cards have been keypunched. Partial analysis of the data has been carried out. Comparison of findings in this project with findings in the Collaborative Study will be carried out at a later time.

Study will be submitted in manuscript form by the end of the calendar year.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-63 PR/OC 1146
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Public Health Implications Study of Perinatal Mortality in the Collaborative Study and in the Collaborative Study Cities.

Previous Title: Revision and Expansion of Previous Project Entitled A Commentary On The Appropriateness Of The Use Of Certain Tabular Data, For Formulating Generalizations Concerning Populations In The Same Cities As Those In Which The Collaborative Study On Cerebral Palsy, Mental Retardation And Other Neurological And Sensory Disorders Of Infancy And Childhood Is Being Conducted.

Previous Serial Number: Same

Principal Investigators: Z.A. Shakhashiri, M.D., PRB, NINDS
Leonard V. Phelps, PRB, NINDS
Glen S. Bartlett, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: The Census Bureau and the National Center for Health Statistics cooperated in the furnishing of necessary statistical information for the United States and cities. The respective state or city health departments are providing natality and mortality data for the Project cities.

Man Years:

Total:	0.50
Professional:	0.30
Other:	0.20

Project Description:

Objectives: To evaluate fetal and infant mortality of the Collaborative Study population and of the cities from which that population is drawn, with the aim of comparing the two populations, city by city, and institution by institution, on mortality characteristics.

Methods employed: In addition to the data previously available from the National Center for Health Statistics for perinatal events, detailed data on natality and perinatal mortality are being sought for the study cities from

either the state or city health departments, whichever has jurisdiction for these records. The data include figures for livebirths, stillbirths, and deaths under 24 hours, 1 day to 7 days, 8 days to 28 days and 1 month to 12 months, evaluated by birthweight, length of gestation, race and sex, and plurality for the years 1959 through 1966. Corresponding data will be compiled by institution for the PRB study population. The state or city health departments have been asked to furnish either completed tabulations or raw data to be tabulated (arrangements finalized) by the PRB Section on Data Management and Retrieval.

Considerable effort has been and is being expended, in connection with the Section on Data Management and Retrieval, PRB, and the Office of Biometry, NINDS, to create a usable data file of the external data being obtained in connection with this study. The aim is to provide a file with more general utility than the limited scope of this study. When such a file is created, the information necessary to make use of the file will be made available to interested persons in PRB.

Major Findings: Evaluation of birthweight and length of gestation data for all core live births (first and subsequent pregnancies) reveals differences between races and between sexes that are generally persistent among all the institutions. Birthweights are lighter among non-whites than among whites, and among females than among males. With white males the heaviest, the order of decline is next white female, then, at about the same weight, non-white males, then non-white females. There is a particular excess of non-whites at low birth weights (2500 grams or less). Length of gestation is shorter among non-white than among whites by about 1 week, with an excess of both short-gestation and long-gestation deliveries among non-whites. Length of gestation is slightly shorter among males than among females in both races, but less consistently so among whites.

Perinatal mortality has declined in the study population since its first year, with a transient elevation in 1962. Group I mortality (fetal deaths 1001 grams and over plus deaths under 7 days of age per 1000 total births) declined from 28.5 in 1959 to 17.6 in 1966 (mean 21.7) among whites and from 33.2 to 21.8 (mean 28.4) among non-whites. Group II mortality (fetal deaths 501 grams and over plus deaths under 28 days per 100 total births) declined from 34.9 in 1959 to 19.1 in 1966 (mean 26.0) among whites and from 39.8 to 25.5 (mean 33.3) among non-whites. These trends tended to persist from institution to institution, though to varying degrees.

Previous deadline could not be met because of delays in receipt of data from the cities and in preparing these data from their various sources into a single program for the computer.

It is anticipated that the file will be created and the present phase of the study completed by the end of June, 1970.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-66 PR/OC 1357
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Prior Pregnancy Loss and Present Infant Outcome

Previous Serial Number: NDS (CF)-66 PR/SA 1357

Principal Investigator: W.S. Jones, M.D.
Brown University, Providence, R.I.

Other Investigators: R.H. Holden, Brown University, Providence, R.I.

Cooperating Units: Perinatal Research Branch, NINDS

Man Years:

Total:	0.4
Professional:	0.2
Others:	0.2

Project Description:

Analysis of 25,000 women indicates that gestational background has prognostic value of statistical significance. Probability of a successful outcome in the current pregnancy, among women with prior reproductive failures, diminishes in very close relationship to the number of previous losses.

Project has been completed.

Paper read at Second Scientific Meeting of the Collaborative Study, March 24-25, 1966, Washington, D.C.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-66 PR/OC 1358
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Dilatation Curves

Previous Serial Number: NDB (CF)-66 PR/SA 1358

Principal Investigator: Kenneth R. Niswander, M.D.,
University of Buffalo, Buffalo, N. Y.

Other Investigators: E. Friedman, M.D.,
Michael Reese Hospital, Chicago, Illinois

Cooperating Units: Perinatal Research Branch, NINDS

Man Years:

Total:	0.6
Professional:	0.5
Other:	0.1

Project Description:

This study, whereas currently in progress, entails the production of dilatation curves from the case records of some 1,000 women whose labors were complicated either by maternal dystocia, fetal dystocia, or uterine dysfunction.

Study has been completed.

Honors and Awards: None

Publications: Friedman, E. A., Niswander, K. R., Sachtleben, M. R. and Nemore, J.: Dysfunctional Labor. VIII. Relative accuracy of clinical and graphic diagnostic methods. Obstet. Gynec. 33:145-152, 1969.

Serial No. NDS (CF)-66 PR/OC 1359
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neonatal Pneumonia in Liveborn Infants

Previous Serial Number: Serial No. NDB (CF)-66 PR/SA 1359

Principal Investigator: Sheldon B. Korones, M.D.
University of Tennessee Medical College
Memphis, Tennessee

Other Investigators: H. Abramson, M.D., New York Medical College,
New York, N. Y.
T. Fujikura, M.D., PRB, NINDS
A. Kantor, Office of Biometry, NINDS

Cooperating Unit: Perinatal Research Branch, NINDS

Project has been discontinued.

Serial No. NDS (CF)-66 PR/OC 1363
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Early Signs of Neurologic Disorders

Previous Serial Number: Serial No. NDB (CF)-66 PR/SA 1363

Principal Investigator: Marguerite J. Gates, M.D.
Columbia University, New York, N. Y.

Other Investigator: Pediatric Staff, Babies Hospital, New York, N. Y.

Cooperating Unit: Perinatal Research Branch, NINDS

Project has been discontinued.

Serial No. NDS (CF)-66 PR/OC 1366
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Incompetent Cervix

Previous Serial Number: NDB (CF)-66 PR/SA 1366

Principal Investigators: Luke Gillespie, M.D.,
Boston Lying-in Hospital, Boston, Mass.
Heinz Berendes, M.D., PRB, NINDS

Other Investigators: J. Deutschberger, Office of Biometry, NINDS
N. Lloyd, PRB, NINDS

Cooperating Unit: Perinatal Research Branch, NINDS

Project has been discontinued.

Serial No. NDS (CF)-66 PR/OC 1369
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Spontaneous Premature Rupture of the Membrane

Previous Serial Number: None

Principal Investigator: R. S. Sappenfield, M.D.,
Charity Hospital, New Orleans, La.

Other Investigators: J. P. Mule, Charity Hospital, New Orleans, La.
H. Berendes, M.D., PRB, NINDS
W. Weiss, Office of Biometry, NINDS

Cooperating Units: Perinatal Research Branch, NINDS

Project has been discontinued.

Serial No. NDS (CF)-66 PR/OC 1371
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Epidemiology of Neonatal Seizures

Previous Serial Number: None

Principal Investigator: W.W. Clark, Jr. M.D.,
University of Oregon, Portland, Oregon

Other Investigators: H. Berendes, M.D., PRB, NINDS
A. Kantor, Office of Biometry, NINDS
J.S. Nemore, PRB, NINDS

Cooperating Units: None

Project has been discontinued.

Serial No. NDS (CF)-66 PR/OC 1377
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Reproductive Wastage in Bronchial Asthma

Previous Serial Number: None

Principal Investigator: Myron Gordon, M.D.
New York Medical College, New York, N.Y.

Other Investigators: K.R. Niswander, M.D., Univ. of Buffalo, N.Y.
H. Berendes, M.D., PRB, NINDS
A. Kantor, Office of Biometry, NINDS
N. Lloyd, PRB, NINDS

Cooperating Units: Perinatal Research Branch, NINDS

Project has been completed.

Honors and Awards: None

Publications: M. Gordon, K.R. Niswander, H. Berendes, and A. Kantor:

Fetal Morbidity Following Potentially Anoxigenic Obstetrical Conditions: VII. Bronchial Asthma. Amer. J. Obstet. Gynec. In Press.

Serial No. NIDS (CF)-66 PR/OC 1378
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Prediction of Birth Weight-Multivariate Analysis

Previous Serial Number: None

Principal Investigator: Heinz W. Berendes, M.D., PRB, NINDS

Other Investigators: W. Weiss, Office of Biometry, NINDS
J. Deutschberger, Office of Biometry, NINDS
Z. Shakhashiri, M.D., PRB, NINDS
E. Jackson, Office of Biometry, NINDS

Cooperating Units: Perinatal Research Branch, NINDS

Man Years:

Total:	0.7
Professional:	0.5
Other:	0.2

Project Description:

In the Collaborative Project, the birth weight of the infant is the best predictor, by far, of neonatal mortality and of almost every characteristic of morbidity in the study.

Birth weight, then, merits intensive investigation. It is fortunate that this variable has attributes conducive to statistical treatment; it is always reported, it is measured with considerable precision and it is continuous over a wide range of values.

This communication reports on two aspects of a study of birth weight. The first is directed towards the identification of those characteristics and conditions of pregnancy which will, most precisely, estimate the birth weight of the infant. The variables studied range in time, relative to the period of pregnancy, from those available prior to the study pregnancy, to those which are measured in the stages of labor and delivery.

The identification of those variables, which, taken together, provide the means for estimating birth weight within narrow limits, may lead to increased understanding of the role of these variables in their association with birth weight.

The practical aspect of prediction--that is, the measure of the availability and contribution of important characteristics for predicting birth weight, by time sequence, during the period of pregnancy, is discussed.

On the basis of the prior examination of study data, a total of 38 variables were selected for a multiple regression study of birth weight.

The birth weights of the children of some 6600 whites and 8000 Negroes, who had at least one prior pregnancy, were evaluated separately by race.

Of the 38 considered, 21 variables and 30 variables, for whites and Negroes respectively, show significant association with birth weight. Despite the larger number of significant variables, the correlation with birth weight is less for Negroes than for whites.

Project is almost complete and will soon be reported.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-66 PR/OC 1379
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Fetal Heart Rate in Relation to Pregnancy Outcome

Previous Serial Number: None

Principal Investigators: Ralph C. Benson, M.D.,
Univ. of Oregon Medical School, Portland, Oregon
H. Berendes, M.D., PRB, NINDS

Other Investigators: F. Shubeck, M.D., Univ. of Oregon Medical School
W. Weiss, Office of Biometry, PRB, NINDS
J. Deutschberger, Office of Biometry, PRB, NINDS
Z. Shakhashiri, M.D., PRB, NINDS

Cooperating Units: None

Man Years:

Total:	0.7
Professional:	0.5
Other:	0.2

Project Description:

Objectives: To identify a fetal heart rate factor which would be a senstitive indicator of fetal distress.

Methods Employed: Fine fetal heart rate factors, which include the lowest rates, the variability in rates, sudden drops in rate, and consecutive drops in rate were compared against indices of fetal mortality and fetal morbidity, as well as morbidity up to one year of age, with such factors as the birth weight, use of anesthesia, stage of labor and number of heart rate observations kept constant.

Major Findings: The fine fetal heart rate variables form a hierarchy in their degree of sensitivity as predictors of fetal distress. The significant associations of these variables appear to be exclusively with stillbirths and neonatal death rates, and with the five-minute Apgar score. Little association is noted with the other indices of morbidity studied.

Study has been completed.

Honors and Awards: None

Publications: Benson, R.C., Shubeck, F., Deutschberger, J., Weiss, W. and Berendes, H.: Fetal heart rate as a predictor of fetal distress. Obstet. Gynec. 32: 259-266, 1968.

Serial No. NDS (CF)-68 PR/OC 1618
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Effect of Labor on the Outcome of the Child

Previous Serial Number: None

Principal Investigators: Z. A. Shakhashiri, M.D., PRB, NINDS
W. Lawrence Holley, M.D., PRB, NINDS
A. A. Lilien, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: Perinatal Research Branch, NINDS

Man Years:

Total:	.08
Professional:	.06
Other:	.02

Project Description:

In order to single out the effect of labor, if any, on fetal growth and development, a study is made of outcomes of normal pregnancies terminated spontaneously, compared to outcomes of similar pregnancies terminated by elective induction of labor and to outcomes of similar pregnancies terminated by elective cesarean section.

Methods Employed: Project infants of normal pregnancies terminated as described above will be compared for selected outcome variables such as mortality, Apgar, bilirubin, mental and motor scores at eight months and I.Q. at four years. All three groups will be controlled for race, birth weight and gestation length.

Major Findings: A search is under way to ascertain whether cases are available in adequate numbers to make the design feasible. Additional non-Project cases might be needed.

Held in abeyance pending updating of data file.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-66 PR/OB 1331
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Obstetric factors in twin pregnancies.

Previous Serial Number: Same

Principal Investigator: Rudolf P. Vollman, M.D., PRB, NINDS

Other Investigators: Jose G. Marmol, M.D., PRB, NINDS
Irene B. Ross, PRB, NINDS

Cooperating Units: All institutions participating in the Collaborative Project

Man Years

Total:	0.3
Professional:	0.2
Others:	0.1

Project Description:

Objectives: The early diagnosis of a twin pregnancy still remains an important problem on which depend the prenatal care and the management of the labor and delivery. The study has two objectives:

1. To study the outcome of twin pregnancies in relation to the time the diagnosis was first established.

2. To make a comparison of the obstetric problems presented by the first versus the second twin and their effect upon the fetal outcome.

Methods: With the help of a computer printout, an established case and card file and an additional review of a current file on abortions and fetal deaths the twins delivered in the Collaborative Project through December 31, 1965, have been identified. All case records were reviewed and additional information or clarification was solicited from the collaborating hospitals as needed. The mother's medical, family and reproductive history, together with information on the course of the Study pregnancy, intercurrent diseases, drugs, obstetric complications, labor and delivery and outcome of pregnancy were abstracted. These data have been used to prepare a set of tabulations

for the study of the variables specified above. The completion of this study has been delayed due to difficulties in completing missing information. Hopefully, it will be completed during the current fiscal year.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-66 PR/OB 1333
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Distribution of abortions by chronologic and gynecologic age of the gravida.

Previous Serial Number: Same

Principal Investigator: Rudolf F. Vollman, M.D., PRB, NINDS

Other Investigators: Annie W. Litz, PRB, NINDS
Jose G. Marmol, M.D., PRB, NINDS
Irene B. Ross, PRB, NINDS

Cooperating Units: All institutions participating in the Collaborative Study

Man Years:

Total:	0.3
Professional:	0.2
Others:	0.1

Project Description:

Objectives: Information is accumulating which demonstrates that endocrine and morphologic conditions for optimal reproductive performance are reached only several years after menarche. The conventional association of pregnancy outcome by chronologic maternal age will be compared with the mother's gynecologic age, based on the age at menarche.

Methods: For Study pregnancies terminating in abortion, a number of important maternal variables will be abstracted from the Study record: race, chronologic and gynecologic age, marital status, gravidity and parity, length of the menstrual cycle, medical and obstetric complications of the Study pregnancy, duration and outcome of the Study pregnancy. These variables will serve as controls in the analysis of chronologic versus gynecologic maternal age. Due to lack of time this study has been delayed, but it will be continued.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-67 PR/OB 1507
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: History of the Maternal Mortality Study Committees in the United States.

Previous Title: The history and present function of the Maternal Mortality Study Committees.

Previous Serial Number: Same

Principal Investigator: Jose G. Marmol, M.D., PRB, NINDS

Other Investigators: Alan L. Scriggins, M.D., PRB, NINDS
Rudolf F. Vollman, M.D., PRB, NINDS

Cooperating Units: None

Man Years

Total:	0.2
Professional:	0.2
Others:	0.0

Project Description:

Objectives: To study the circumstances that led to the establishment of the Maternal Mortality Study Committees in the U.S.A., their contribution to the decline in maternal mortality rates, their present status and future role in maternal health.

Methods: A form letter was sent to the secretary of the State Medical Society of all of the states with the following questions: Does your state have a Maternal Mortality Study Committee? 2) When was the committee formed and how does it operate? 3) What is the accepted definition of maternal mortality in your state and is it uniformly applied? Supplementary information was obtained by reviewing the journals of the State Medical Societies and by personal communication with some of the obstetricians involved in the creation of these committees. The information was tabulated for each state and submitted to the secretaries of the State Medical Societies for correction or confirmation.

Findings: Forty-four states and the District of Columbia presently conduct maternal mortality studies. Six states do not have a Maternal Mortality Committee. Thirty-eight of the states have worked without interruption. Twenty-eight states have legislation protecting the maternal mortality investigators from malpractice suits. Most of the committees have adopted the definitions and instructions given in the Guide for Maternal Death Studies by the American Medical Association. The composition of the committees varies from state to state as does the frequency of their meetings and the types of publications of their findings. The committees collect information by mailed questionnaire and/or by personal interviews conducted by a physician.

The Mortality Study Committees of the State Medical Societies operate in close cooperation with the state health departments. In 21 states and the District of Columbia either the director or the consultant of the Maternal and Child Health Division is also a member of the committee. Some large states also have local county Maternal Mortality Study Committees. Several authors attest the important contribution of these committees in the reduction of maternal deaths. Due to the low maternal mortality rate, many of the Maternal Mortality Study Committees have turned their attention to the problems of maternal morbidity, perinatal mortality and obstetric problems such as: causes of obstetric complications, the use of drugs during labor, the injudicious induction of labor, etc. Canada and Israel have followed this approach in the investigation of maternal mortality.

Project has been completed.

Honors and Awards: None

Publications: Marmol, J.G., Scriggins, A.L., and Vollman, R.F.: History of the maternal mortality study committees in the United States. Obstet. Gynec. (In press).

Serial No. NDS (CF)-68 PR/OB 1619
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Obesity and pregnancy in the Collaborative Project.

Previous Title: Obesity in pregnancy in the Collaborative Project.

Previous Serial Number: Same

Principal Investigator: Arnold A. Lilien, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years

Total:	0.08
Professional:	0.04
Others:	0.04

Project Description:

Objectives: To resolve whether maternal obesity increases perinatal risk. Further, to identify and characterize those factors contributing to this risk.

Methods: A printout with the NINDB numbers of all gravidae in the Collaborative Project who weighed 200 lbs. or more at the time of their first clinic visit were reviewed. The plan was to hand-check the records of these gravidae for maternal, fetal and obstetrical factors as well as outcome.

Major Findings: Preliminary results show no increase in perinatal mortality in this group. However, the number of cesarean sections seems to be higher among the obese gravidae. The project remains in the analysis stage.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/OB 1620
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Oxytocin-induced water intoxication.

Previous Serial Number: Same

Principal Investigator: Arnold A. Lilien, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years

Total:	0.2
Professional:	0.2
Others:	0.0

Project Description:

Objectives: To report a maternal death caused by a side reaction to a commonly used drug, oxytocin.

Methods: A case treated at the Bronx Municipal Hospital for an uncomplicated, incomplete abortion in November 1966 by the author was reviewed for publication. This included a review of the pertinent literature.

Major Findings: Oxytocics administered over a period of time will cause water retention. This can seriously impair water and electrolyte balance. The first reported maternal death due to oxytocin water intoxication is described. Project has been completed.

Honors and Awards: None

Publications: Lilien, A.A.: Oxytocin-induced water intoxication. Obstet. Gynec. 32: 171-173, 1968.

Serial No. NDS (CF)-68 PR/OB 1621
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Term intrapartum fetal death.

Previous Title: Term intrapartum fetal demise.

Previous Serial Number: Same

Principal Investigator: Arnold A. Lilien, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years

Total:	0.46
Professional:	0.33
Others:	0.13

Project Description:

Objectives: To identify and characterize the maternal, fetal and obstetrical factors which are responsible for death of the term fetus during labor.

Methods: A hand-review of all the records of term fetal and neonatal deaths up to 24 hours was done to isolate that group which died during labor. The group so defined was then reviewed for maternal, fetal and obstetrical factors which were responsible for the death. The results were compared to a liveborn control group matched for race, age, hospital, date of delivery and fetal sex.

Major Findings: Approximately 50% of term intrapartum fetal deaths cannot be explained by the data in the record. Found to be important in these deaths were breech presentation, tight nuchal cord, prolonged gestation, prolonged rupture of membranes and prior stillbirth.

Paper to be presented at the annual meeting of the American College of Obstetricians and Gynecologists, Bal Harbour, Florida, April 28-May 1, 1969, and has been submitted for publication in the American Journal of Obstetrics and Gynecology.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/OB 1622
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Mothers of mongoloid infants in the Collaborative Project.

Previous Title: Mothers of mongoloids in the Collaborative Project.

Previous Serial Number: Same

Principal Investigator: Jose G. Marmol, M.D., PRB, NINDS

Other Investigators: Alan L. Scriggins, M.D., PRB, NINDS
Rudolf F. Vollman, M.D., PRB, NINDS

Cooperating Units: None

Man Years

Total:	0.7
Professional:	0.5
Others:	0.2

Project Description:

Objectives: To identify possible obstetric and medical factors (including x-rays and drugs) that characterize mothers of mongoloids in comparison with a matched control group.

Methods: Comparison and evaluation of incidences of medical and obstetric complications in mothers of mongoloids with a matched control group.

Major Findings: The incidence of mongolism in whites and Negroes is nearly equal. The distribution of incidence by age is bimodal. There are more white mothers of mongoloid infants in the younger age groups and more Negroes in the older age groups. There is essentially no difference in parity, pregnancy-free interval, number of prior abortions, or medical history between the Study and control groups. Both the birthweight and the duration of pregnancy are slightly less for the Study group than for the controls. There are more male than female mongoloid infants. The similar drug and x-ray experience of the Study and control groups is noted.

Project has been completed.

Honors and Awards: None

Publications: Marmol, J.G., Scriggins, A.L., and Vollman, R.F.: Mothers of mongoloid infants in the Collaborative Project. Amer. J. Obstet. Gynec. (In press).

Serial No. NDS (CF)-68 PR/OB 1623
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Prenatal drugs.

Previous Serial Number: Same

Principal Investigator: Alan L. Scriggins, M.D., PRB, NINDS

Other Investigators: Rudolf P. Vollman, M.D., PRB, NINDS
Seymour Katsh, Ph.D., University of Colorado Medical Center
S. Barbara Katz, Office of Biometry, NINDS

Cooperating Units: All institutions participating in the Collaborative Study

Man Years:

Total:	0.1
Professional:	0.1
Other:	0.0

Project Description:

Objectives: To compare and contrast the reporting of different kinds of drugs in the total core population of the Collaborative Project.

Methods: A classification of all prenatal drugs coded by the Collaborative Project was devised which encompasses distinctions into unknowns and knowns and then single chemical entities and combination drugs. Knowns are then subdivided into groups thought to be most meaningful for the clinician (e.g. single/anti-infective/antibiotic and single/anti-infective/sulfonamide etc.) by PRB personnel with clinical backgrounds. A pharmacologist, acting as a consultant, also reviewed the classification. A program is being devised to present the reporting of such groups of drugs by race, hospital and trimester. Another aspect of the study will be a description of the sample reporting drugs (and no drugs) by race, age and hospital. Further, the number of specific drugs reported will be related to the time of registration in the Collaborative Project for prenatal care. Utilizing the classification provided by clinicians and pharmacologist, the data will be tabulated as above by computer facilities.

Significant Findings: Six per cent of the study gravidae reported no drugs during pregnancy. The number of drugs reported during pregnancy depends upon the weeks of gestation when a gravida registers for prenatal care and upon the hospital. Younger gravidae reported fewer drugs than older gravid Within the study hospitals there is no difference by race in drug reporting. The median number of drugs reported per gravida varies between 2 and 4, in any one hospital. However, more than 6 drugs per gravida have been reported. Analgesics, sedatives, antihistaminics and antinausiants, tranquilizers and antibiotics are most frequently reported, but the types encountered represent in fact all substances that can be defined as pharmacologic agents.

The study is being prepared for publication and was presented at the annual meeting of the Society for Gynecologic Investigation, Denver, Colorado, March 20-21, 1969.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/OB 1624
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Respiratory distress syndrome in babies born to mothers reporting acetazolamide during the labor and delivery period.

Previous Serial Number: Same

Principal Investigator: Alan L. Scriggins, M.D., PRB, NINDS

Other Investigators: Arnold A. Lilien, M.D., PRB, NINDS

Cooperating Units: Charity Hospital, New Orleans and the Medical College of Virginia

Man Years

Total:	0.2
Professional:	0.1
Others:	0.1

Project Description:

Objectives: To investigate the possible relationship between depression of the enzyme carbonic anhydrase and the respiratory distress syndrome in newborns.

Some investigators have noted depressed carbonic anhydrase in newborns with R.D.S. compared to controls. Since acetazolamide, a diuretic, acts by depression of that enzyme, it was thought that maternal ingestion of acetazolamide during labor might result in a higher rate of R.D.S. in their babies. Thus a hand-review of approximately 300 cases reporting acetazolamide (divided nearly equally between two collaborating institutions) showed only 2 cases of R.D.S. The study has been completed.

Findings: Due to the small number of cases with R.D.S., a possible association between the drug and R.D.S. cannot be evaluated.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/OB 1625
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Menstruation and ovulation in the monkey.

Previous Serial Number: None

Principal Investigator: Rudolf F. Vollman, M.D., PRB, NINDS

Other Investigators: Irene B. Ross, PRB, NINDS

Cooperating Units: Department of Embryology, Carnegie Institution of Washington

Man Years

Total:	0.1
Professional:	0.1
Others:	0.0

Project Description:

Objectives: To systematically analyze all the unpublished data collected by the late Dr. Carl G. Hartman on reproduction in the monkey.

Methods: Tabulate and analyze data on menstruation, ovulation, mating, conceptions, duration of pregnancy, birthweights, lactation and steroid hormone treatment in the monkey.

Progress in the analysis of the data has been slowed down due to the reduction in manpower.

Honors and Awards: Memorial address in honor of Dr. Carl G. Hartman at the Second International Congress of Primatology, Atlanta, Georgia, June 30-July 3, 1968.

Publications: None

Serial No. NDS (CF)-68 PR/OB 1626
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Distribution of fertile and sterile coitus by days of the menstrual cycle.

Previous Serial Number: None

Principal Investigator: Rudolf F. Vollman, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years

Total:	0.3
Professional:	0.2
Others:	0.1

Project Description:

Objectives: To identify the optimal time of conception in women.

Methods: Calendar records on menstruation, intercourse, basal body temperature during the menstrual cycle and pregnancy.

Major Findings: Conceptions after single intercourse by day of the menstrual cycle do not provide an estimate of the time of ovulation because of the variability in the length of the postmenstrual phase. When the point of reference is the rise of the basal body temperature, conceptions still occur within a range of 10 days and conception rates per day do not reach 20 percent, even on the optimal day. This astonishingly low rate of conceptions clearly indicates that further research in the processes of ovulation, fertilization and implantation in the human is required.

Paper to be presented at the International Meeting of Obstetrics and Gynecology in New York, N.Y.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/OB 1734
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Premature intrapartum fetal death.

Previous Serial Number: None

Principal Investigator: Arnold A. Lilien, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	0.28
Professional:	0.20
Others:	0.08

Project Description:

Objectives: To ascertain what are the causes of fetal death in the intrapartum period among prematures.

Methods: Hand-review of all labor and delivery events in fetal deaths weighing 501-2500 gms to define the study group. Case study and comparison with a control group is then planned.

Major Findings: Project is an extension of the one entitled "Term intrapartum fetal death" and is in progress.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-63 PR/PN 1162
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Apgar Scores

Previous Serial Number: Same

Principal Investigator: Joseph S. Drage, M.D., NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.20
Professional:	.10
Other:	.10

Project Description:

This study has matched one and five-minute Apgar scores of children to their performance on the four-year psychological examination. Children with certain congenital malformations have been excluded. Controls for this study are birthweight, education of gravida, race, and sex. The outcome on the four-year psychological examination is defined by the Binet I.Q. score, the Graham Block Sort Raw Scores, the assessment of fine and gross-motor development, the behavior profile, and the overall impression. Study in progress - data feedback obtained and undergoing analysis.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-63 PR/PN 1163
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: An Investigation into the Relationship Between Congenital Heart and Great Vessel Anomalies and Selected Factors as Recorded in the Collaborative Perinatal Research Project

Previous Serial Number: Same

Principal Investigators: Lenore Bajda, M.D., PRB, NINDS
Sheila Mitchell, M.D., Office of the Director, NIH

Other Investigators: Heinz W. Berendes, M.D., PRB, NINDS
John L. Sever, M.D., PRB, NINDS

Cooperating Units: Office of the Director, NIH

Man Years:

Total:	.33
Professional:	.33
Other:	.00

Project Description: The primary objective of this study is to assess relationships between certain maternal variables and congenital heart-great vessel anomalies.

Additional objectives include investigating relationships between early signs of abnormality and the existence of definitive congenital heart lesions and determining the existence of congenital heart-vessel anomaly in conjunction with mental retardation as recorded in the eight-month psychological examination, the one-year summary records, four-year psychological examination, and seven-year neurological and psychological examinations.

To date, maternal parameters analyzed included age of gravida, parity, prior pregnancy outcome, prior and current health status, ABO blood group, current smoking pattern, and viral antibody status.

Study data was obtained from Collaborative Study records received by PRB from the onset of the Study (January 1959) through December 1964. These records provided 112 live and stillbirth cardiac cases for study out of a population pool of approximately 38,000. Analysis of an expanded Study cohort through 1965, with a population pool of approximately 55,000 providing additional cases, is underway in anticipation that the additional cases will support earlier findings and perhaps provide further clues for identifying etiological relationships.

Major Findings:

There was a definite preponderance of mothers over 30 in the C-V Study group. Controlling for race, and removing cases with chromosomal aberrations, there were more white mothers in the 30 and over age group than expected at the .05 level. This trend is also noted among Negroes. There was a greater than expected number of gravida with systemic disease complications and prior pregnancy loss among the mothers of the cardiacs. A breakdown of these factors for greater specificity is pending.

Because the number of patients with each specific cardiac abnormality was small, specific associations between serological findings and clinical observations were not possible, although several interesting trends were noted. Further analysis with additional patients is under way.

A preliminary report on the 1964 cohort study was presented at the 1966 Annual Meeting of the Teratology Society.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-63 PR/PN 1164
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Early Signs as Predictors of Death and Neurological Abnormality Among Premature Infants Weighing 1000-2000 Grams.

Previous Serial Number: Same

Principal Investigator: Joseph S. Drage, M.D., PRB, NINDS

Other Investigators: Karin B. Nelson, M.D., PRB, NINDS
Heinz Berendes, M.D., PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.16
Professional:	.08
Other:	.08

Project Description:

A group of 720 single liveborn premature infants with birthweights of 1000-2000 grams has been prospectively studied relating the presence of specific neurological signs during the nursery period to neurological status at one year of age. Of the 720 infants, 485 were examined at one year, 159 died during the first year, and 76 were lost to follow-up. There were 101 neurologically abnormal infants among the 485 examined at one year. The first four PED-2's (Neonatal Pediatric Examinations) were reviewed for the presence or absence of early signs. Among the 720 infants, 78.2% received four or more PED-2 examinations while 100.0% of the abnormals and 94.8% of the normals received four or more examinations. Many of the deaths were in the first 24 hours of life, and most of the infants receiving zero, one, or two PED-2 examinations were deaths. A positive early sign was defined as the occurrence, on at least one examination, of the specific early sign being studied. Specific signs studied included cry, suck, palmar grasp, traction response, Moro reflex, eye movement, muscle tone, local convulsions, general convulsions, highest serum bilirubin, Coombs' test, procedures of resuscitation, etc. Each of these signs was considered separately, and those showing significant association with death and abnormal outcome were then combined. When three signs were considered in combination, the more that were positive the greater the association of neurological abnormality and death, and of neurological abnormality alone.

This study is now being up-dated on the entire study sample to include some 1400 cases.

Honor and Awards: None

Publications: None

Serial No. NDS (CF)-65 PR/PN 1271
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Effects of Maternal Rubella on the Child

Previous Title: Effects of Maternal Rubella as Evaluated in the One-Year-Old Child

Previous Serial Number: Same

Principal Investigators: John L. Sever, M.D., PRB, NINDS
Janet Hardy, M.D., Johns Hopkins Hospital, Baltimore, Maryland
Karin B. Nelson, M.D., PRB, NINDS
Mary R. Gilkeson, PRB, NINDS

Other Investigators: None

Cooperating Units: Section on Infectious Diseases

Man Years:

Total:	0
Professional:	0
Other:	0

Project Description: Follow-up continues of pregnancies occurring during the 1964 epidemic of rubella. A recently prepared paper deals with clinical and laboratory findings in children through the age of three years, and it is planned that after the four-year examinations are available a detailed report including clinical and serologic information will be undertaken. Complete serologic information for all patients will soon be available, enabling the identification of many of the gravidae with subclinical disease and study of their pregnancy outcomes. Planning is now in progress for this effort.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-66 PR/PN 1335
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Mortality and Morbidity Among Infants Weighing 1000-2000 Grams.

Previous Serial Number: Same

Principal Investigator: Joseph S. Drage, M.D., PRB, NINDS

Other Investigators: Karin B. Nelson, M.D., PRB, NINDS
B. H. Williams, M.D., PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.17
Professional:	.08
Other:	.09

Project Description:

A group of 720 liveborn infants, with birthweights ranging from 1000-2000 grams, has been studied regarding outcome within the first year of life. This group of 720 infants represents approximately 2% of the group of 35,000 single live births from which they were drawn.

Within the group of 720 infants, 485 were examined at one year of age, and of these 101 were considered to have definite neurological abnormality. There were 159 deaths during the first year of life. Thus, 260 of the 720 infants either died during the first year of life or were considered neurologically abnormal by examination at one year. There were 76 infants lost to follow-up and this represents 10% of the original 720 cases. Over 50% of the 159 deaths occurred during the first 24 hours and over 90% occurred during the first 28 days.

The 101 infants neurologically abnormal at one year were classified in the following way: isolated motor retardation, diplegia, hemiplegia, quadriplegia, monoplegia, athetosis, motor retardation with neurological signs insufficient for other diagnosis, and other (infants with neurological signs, but not fitting a specific diagnostic category). Congenital malformations were also monitored for this group.

Outcome at one year (death, abnormal, normal, and lost) was then tabulated within each 100-gram birthweight interval. In general for the 720 infants,

as the birthweight increased, the percent of deaths decreased. For infants in jeopardy (dead or abnormal at one year), the same relationship held. The percent of lost cases within each 100-gram birthweight interval varied slightly.

Study in Progress.

This study sample is currently being increased to include some 1400 infants.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-66 PR/PN 1337
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: An Investigation into Relationships Between History of Signs, Symptoms and Behavior Early in Pregnancy and Pregnancy Outcomes.

Previous Serial Number: Same

Principal Investigators: Lenore Bajda, M.D., PRB, NINDS
Rudolf Vollman, M.D., PRB, NINDS
Sarah H. Sledge, Ph.D., PRB, NINDS

Other Investigators: Laverne C. Edmondson, Statistical Assistant, PRB, NINDS

Discontinued because of basic analysis program.

Serial No. NDS (CF)-66 PR/PN 1338
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Association of Mental Subnormality with Head Circumference, Congenital Malformations, and Other Conditions of the Newborn Term Infant

Previous Serial Number: Same

Principal Investigator: Lenore Bajda, M.D., PRB, NINDS

Other Investigators: Karin B. Nelson, M.D., PRB, NINDS
Jerome Deutschberger, OB, NINDS

Cooperating Units: Office of Biometry

Man Years:

Total:	.08
Professional:	.08
Other:	.00

Project Description: The objective of this study was to determine the relationship between head size and certain other physical features of the Collaborative Study child noted shortly after birth, at the one-year examination and at 4 years upon completion of the psychological examination. The project was in abeyance pending updating of the data file. Meanwhile Dr. Nelson and Mr. Deutschberger have completed their study on "Head Size at One Year as a Predictor of Four-Year IQ" (PR/PN 1509) using a sample of the Collaborative Study population including a partially selected pediatric group of 9,379 children. They concluded that there is approximately a 50% chance of an IQ of less than 80 at 4 years of age for the one-year male with a head size less than 43 cm and a one-year female with a head size of less than 42 cm. Plans are under way to examine in detail the low and high head measure sample of the Nelson-Deutschberger Study for other factors which might account for the correlation between head size and the four-year IQ values. Depending on the results of this analysis, the original study proposal will then move either forward with a larger sample or terminate.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-66 PR/PN 1339
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Sudden Unexpected Death.

Previous Serial Number: Same

Principal Investigator: Joseph S. Drage, M.D., PRB, NINDS

Other Investigators: Toshio Fujikura, M.D., PRB, NINDS
Lon White, M.D., PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.16
Professional:	.08
Other:	.08

Project Description:

Some 207 cases of sudden death among 36,000 Collaborative Study children where the death occurred outside of a hospital have been reviewed regarding the cause. There were 90 cases autopsied where no cause of death was found. There were 34 deaths where the cause of death was known and 86 cases where the death was sudden and unexplained but no autopsy was performed.

The frequency distribution of the socioeconomic indices of the 90 cases of autopsied sudden unexplainable deaths was significantly lower than that of the index for all 36,000 study children. For the deaths of known cause, the frequency distribution of socioeconomic indices was essentially super-imposed on the distribution of the 36,000 study children.

The purpose of this study is to investigate the early neonatal course of these sudden unexplainable deaths for evidence of abnormality or instability which could differentiate this group from a group of controls matched for hospital, sex, race, and birthweight. Data is being reviewed regarding the time of first breath, time of first cry, need for resuscitation, Apgar score at 1 and 5 minutes, staining of skin and umbilicus, need for special environmental conditions, temperature variation, abnormalities of cry, activity, respiration, color, feeding, and the presence of seizures. Laboratory data regarding ABO blood type, Rh type, lowest hemoglobin, highest bilirubin were also evaluated.

Study is still in progress.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-66 PR/PN 1345
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Influencing Factors in Sudden Unexpected Death

Previous Serial Number: NDB (CF)-66 PR/P 1345

Principal Investigators: Toshio Fujikura, M.D., PRB, NINDS
Joseph Drage, M.D., PRB, NINDS

Other Investigators: Luz A. Froehlich, M.D.

Cooperating Units: None

Man Years:

Total:	.10
Professional:	.08
Other:	.02

Project Description:

Objectives: Sudden unexpected death in infancy presents a serious unsolved problem. It accounts for over 10% of infant mortality in the United States and 20% in England. In the majority of cases, the pathologic findings are minimal. Previous exhaustive studies have concentrated on the neonatal and postnatal conditions. The purpose of this study is to investigate all possible influencing factors on sudden death, especially prenatal and maternal problems which have not been explored in previous studies. Two hundred and seven cases of sudden unexpected deaths in the collaborative study material were identified. The possible influence of the following factors will be investigated: sex, race, birthweight, gestation, placental weight, placental infection, autopsy findings, maternal diseases, type of feeding, Apgar score and socio-economical factors.

Methods Employed: Sudden death cases were divided according to the following:

a. Sudden Unexplainable Death (SUD). Autopsy findings were minimal and could not adequately explain death. 96 cases.

b. Sudden Explainable Death (SED). Death was sudden but autopsy findings were adequate to explain death. 37 cases.

c. Mixed Sudden Death (MSD). Consisted on non-autopsied cases or known autopsied cases where protocol had not yet been received at PRF. 68 cases.

The proportion of SUD to SED cases was obtained in the white and the Negro, and the MSD cases were divided and added onto the corresponding groups using this proportion.

Major Findings: (1) SUD cases were largely premature, not so much in birthweight (white 18.2%, Negro 25.8%) as in gestational age (white 31.0%, Negro 43.9%). Percentage of placentas weighing less than 400 grams was also higher in the SUD group in both white and Negro compared to controls (single live births or SLB). (2) Majority of SUD's occurred between 1-4 months of age and very rarely after six months. (3) Most of the SUD's occurred in the winter months. (4) The peak of SUD cases occurred in somewhat lower socioeconomic strata compared to the general collaborative study population in both white and Negro. (5) Pediatric factors (Apgar score, type of feeding, etc.) and obstetric factors (maternal diseases during pregnancy) are in process. (6) Estimated incidence:

SUD (Sudden Unexplainable Death)

White 2.1 per 1,000 births (25,071 births)
Negro 3.3 per 1,000 births (24,786 births)
White 39.7 per 100 infant and child deaths (136 deaths)
Negro 34.3 per 100 infant and child deaths (242 deaths)

SED (Sudden Explainable Death)

White 0.7 per 1,000 births
Negro 1.2 per 1,000 births
White 14.7 per 100 infant and child deaths
Negro 12.4 per 100 infant and child deaths

Proposed Course: The pathology portion of the study on sudden unexpected death is completed. The evaluation of clinical data by the Section on Pediatric Neurology is still in progress.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-67 PR/PN 1509
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Head Size at One Year as a Predictor of Four-Year IQ

Previous Title: One-Year Head Circumference in Relation to IQ at Four Years

Previous Serial Number: Same

Principal Investigators: Karin B. Nelson, M.D., PRB, NINDS
Jerome Deutschberger, OB, NINDS

Other Investigators: None

Cooperating Units: Office of Biometry

Man Years:

Total:	.35
Professional:	.35
Other:	.00

Project Description: The relationship between head circumference and body length at 50-54 weeks was studied relative to IQ at four years in 9379 children, including all white and Negro children examined within the time intervals set and excepting only those with definite cyanotic heart disease. Control variables were race, sex, and maternal education.

IQ at four years was found to vary directly with head circumference and with body length at one year, and with maternal education, the last-named factor being the most potent. At any given head circumference, including the very small, four-year IQ rose with increasing body length suggesting that the clinical practice of appraising head size with reference to the "proportionality" of head to body size requires re-evaluation.

Contrary to previous reports, head sizes in the smallest 0.67% of the population were associated with four-year IQ's below 80 in only half the cases. The one percent of children with largest heads at one year had four-year IQ's somewhat higher than children whose head sizes were at the mean, and more of the largest-headed children had IQ's of 120 or more at four years.

Nobody with head circumference below 43 cm. or girl with head circumference less than 42 cm. at one year achieved a four-year IQ of 120 or better, and very few male children with one year head circumferences of less than 44 cm. achieved a four-year IQ of 120 or more. This study has been completed and a manuscript has been submitted for publication.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-68 PR/PN 1627
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neuropsychologic Outcome of Children Whose Mothers Were Given Tetracycline During Pregnancy

Previous Serial Number: Same

Principal Investigators: Lawrence E. Gershon, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.20
Professional:	.15
Other:	.05

Project Description: It was hypothesized that tetracycline may reduce the amount of bacterial interference so that utilization of amino acids for fetal development may be increased. It was considered possible that this drug might interfere with intermediary metabolism and adversely affect the fetus. To determine the possible effects, a case listing of all those women reported to have received tetracycline was requested. The cases were hand-reviewed and matched to controls by institution, race, sex, maternal age and parity.

It was found that the children of mothers who received tetracycline were, as a group, 5.1 Binet IQ points higher than their controls. The data, when subject to t-tests, had a p of .001. The results of this analysis are being prepared for publication.

An analysis of the height and weight of these children at 1 year was undertaken, but no significant difference was found.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-68 PR/PN 1628
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Effects of Prenatal Protein Deprivation on Behavior and Brain Structure of Mice

Principal Investigators: John A. Churchill, M.D., PRB, NINDS
J. H. Carleton, M.D., PRB, NINDS
W. Lawrence Holley, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.5
Professional:	.3
Other:	.2

Project Description: Previous studies have shown that deprivation of protein during pregnancy in rats results in full-term but small offspring with impaired ability on learning measures. There has also been suggestive evidence of microscopic structural differences in the brains of the Study animals.

The present study was designed to replicate, in a certain strain of mice, the behavioral effects noted in the rats. After the mice have been tested for learning ability, the mice will be sacrificed and the brains examined with an electron microscope to determine structural changes, if any. The group of mice consists of approximately 50 mice in each of the following groups: mice born to female mice fed a high protein diet during gestation; mice born to female mice with a normal protein diet; and mice born to female mice with a protein-deficient diet during gestation.

The strain of mice chosen has turned out to be unsatisfactory for the learning tests utilized. A different strain of mice is being bred at the present time for use in this study.

The study is still in progress at this time.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/PN 1629
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH

Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Effect of Maternal Hypertension on the Neuropsychological Outcome of the Child

Previous Serial Number: Same

Principal Investigators: W. Lawrence Holley, M.D., PRB, NINDS
Heinz W. Berendes, M.D., PRB, NINDS
John A. Churchill, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.25
Professional:	.20
Other:	.05

Project Description: Many investigators have studied the effects of hypertension in a pregnant woman. At the present time, there is still disagreement about the effects either to the mother or the offspring. This study attempts to verify what effect, if any, hypertension without proteinuria has on the neuropsychological outcome of the child.

Cases were obtained by selecting all single livebirths from the Collaborative Project study children, who had been given the Binet IQ at 4 years of age. The criteria for hypertension was a diastolic blood pressure of greater than 110 mm. Hg. Controls were chosen to have similar socio-economic index, sex, parity and race but who had no diastolic blood pressure greater than 90 mm. Hg.

The tabulation which has been completed, at this time, indicates that hypertension has no significant effect on the neuropsychological outcome of the child. We are reviewing the individual charts, at the present time, to exclude any other factors affecting the neuropsychological outcome of either the cases or the control.

A further search of the data file with computer matched controls is being completed at this time.

The study is in progress at this time.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-68 PR/PN 1630
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Effect of Maternal Hypertension with Proteinuria on the Neuropsychological Outcome of the Child

Previous Serial Number: Same

Principal Investigators: W. Lawrence Holley, M.D., PRB, NINDS
Heinz W. Berendes, M.D., PRB, NINDS
John A. Churchill, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.50
Professional:	.30
Other:	.20

Project Description: There is general agreement that toxemia of pregnancy has unfavorable effects on the child. This relationship has never been fully defined except that children born to toxemic women have a greater incidence of prematurity. There have also been studies indicating central-nervous system impairment. This study relates toxemia (defined in this study as diastolic blood pressure greater than 110 mm. Hg. with at least 3+ albuminuria) to neuropsychological deficits measured by the Bayley developmental scores at 8 months, the Binet IQ at 4 years of age.

Publication Review Board criticized the method of choosingcontrols. Therefore, a new request was submitted to the systems analysis section to retrieve all cases meeting criteria including the most recent updating of the data file. At the same time, controls were to be chosen by computer matching in order to eliminate any possibility of bias. Due to technical difficulties and delay in data retrieval, the revised data is not yet available for analysis.

The Study is in progress at this time.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-68 PR/PN 1631
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neuropsychologic Outcome of Children Whose Mothers Had Proteinuria During Pregnancy

Previous Serial Number: Same

Principal Investigators: Arthur L. Rosenbaum, M.D., PRB, NINDS
John A. Churchill, M.D., PRB, NINDS

Other Investigators: Zekin A. Shakhashiri, M.D., PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.20
Professional:	.15
Other:	.05

Project Description: Animal experimentation has demonstrated a generally poor outcome for the newborn when the mother has been deprived a dietary protein during pregnancy. Offspring of protein deprived rats are smaller in size and have depressed learning abilities. Protein-calorie restriction in weanling animals has been shown to result in stunting, changes in brain composition, and specific neuronal abnormalities.

Less is known about the effect of maternal protein deprivation on the human fetus. The suggestion has been made that some babies born small for their gestational ages, such as twins, may have suffered protein impoverishment. Organ size in fetuses judged small for gestational age seem to be decreased.

Protein loss during pregnancy may have effects on the developing fetus similar to those of low protein intake. This study was designed to examine the effects of maternal proteinuria on psychological and neurological outcomes in the child.

The offspring of women with heavy proteinuria and without hypertension during the second half of pregnancy were matched with "non-proteinuric" control cases. 53 case pairs were thus selected, and the following outcome variables were studied:

A. Duration of Pregnancy
B. Birthweight
C. Bayley mental and motor scores given at 8 months of age
D. The Binet IQ given at 4 years of age
E. A rating scale for postural control observed at 1 year of age

The offspring of the 51 mothers with proteinuria (P) differed significantly from matched cases without proteinuria (C) in the Bayley Mental scores obtained when the children were 8 months of age, the posturing rating scale observed at 12 months of age, and the Binet IQ administered at 4 years of age. Neurologic abnormalities, other than the posturing scale, occurred in 5 offspring of proteinuric and in 1 of non-proteinuric mothers. There was no overall significant difference between the two groups in birthweight or duration of pregnancy. However, birthweights of all groups except the non-white female subjects were significantly lower than their matched controls, $p = <.05$, by Chi-Square analysis.

Honors and awards: None

Publications: Rosenbaum, Arthur L., Churchill, John A., Shakhashiri, Zekin A., and Moody, Richard L.: Neuropsychologic Outcome of Children Whose Mothers Had Proteinuria During Pregnancy. Obstet Gynec. 33: 118-123, 1969.

Serial No. NDS (CF)-68 PR/PN 1632
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neuropsychologic Outcome of Children Born Via the Occiput Posterior Birth Position

Previous Serial Number: Same

Principal Investigators: Arthur Rosenbaum, M.D., PRB, NINDS
Lee Willerman, Ph.D., PRB, NINDS
John A. Churchill, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.20
Professional:	.15
Other:	.05

Project Description: It is well known that there is an increased incidence of mortality and morbidity among children born via the OP birth position. This study was designed as a long-term neuropsychological follow-up evaluation of these children.

Approximately 200 cases of live-born babies delivered in the OP position were studied and compared with a group of children born via the OA position. All cases were from one of the institutions in the Collaborative Perinatal Research project. The two groups were then compared in relationship to the following outcome variables: a) Birthweight, b) Bayley mental and motor scores given at 8 months of age, c) The Binet IQ given at 4 years of age, d) Neurologic abnormalities evaluated at 1 year of age.

The above outcome variables were also studied by subdividing the entire group of OP births into the following categories: a) Spontaneous OP delivery, b) Mid-forceps rotation, c) Manual rotation, d) Length of time during labor the child remained in the OP position.

Analysis of data is still in progress

Presented at Conference on "Physical Trauma as an Etiological Agent in Mental Retardation" Lincoln, Nebraska, October 13-16, 1968.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-68 PR/PN 1633
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neuropsychologic Outcome of Children with Retinal Hemorrhages at Birth

Previous Serial Number: Same

Principal Investigators: Arthur L. Rosenbaum, M.D., PRB, NINDS
John A. Churchill, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.30
Professional:	.20
Other:	.10

Project Description: Retinal hemorrhages in the newborn occur in approximately 20% vertex births. Much work has been done to elucidate the etiology of these hemorrhages, but little is known about their significance in terms of long term follow-up. This study was designed to study the neuropsychologic outcome of children with retinal hemorrhages, and also the relationship between laterality of the hemorrhage and birth position.

Approximately 200 cases of retinal hemorrhage in the newborn were studied, and matched with "non-hemorrhage" controls. These matched pairs were then compared in relationship to the following outcome variables: a) Birthweight, b) Bayley mental and motor scores given at 8 months of age, c) The Binet IQ given at 4 years of age.

The retinal hemorrhage cases were also reviewed in an attempt to analyze the possibility of a relationship between birth position and the eye in which the hemorrhage occurred.

The study is still in progress.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-68 PR/PN 1634
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Etiological Factors in Spastic Diplegia

Previous Title: Spastic Diplegia of Prematurity

Previous Serial Number: Same

Principal Investigators: John A. Churchill, M.D., PRB, NINDS
Jack Carleton, M.D., PRB, NINDS
Heinz Berendes, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.25
Professional:	.15
Other:	.10

Project Description: From the Collaborative Project population of 55,000 cases, all premature infants weighing less than 2.0 Kg. who survived to have neurological examinations at 1 year of age were selected for the present investigation (N=969). The neurological findings were classified by means of a rating scale designed arbitrarily as indicators of bilateral corticospinal tract dysfunction, into definitely spastic diplegic (N=40); mildly spastic diplegic (N=88); and non-spastic (N=835) groups.

Previously, it had been found that spastic prematures had greater postnatal losses in weight than non-spastics. The present study confirmed this finding.

But, surprisingly, in the face of this greater postnatal weight loss, hematocrits obtained within the first 5 days of life (mean age 2.4 days) of spastic prematures were found to be significantly lower than in non-spastics. Hematocrits had been performed on 40 spastic cases, the mean value being 45.7% compared with the mean hematocrit of 54.4% on 643 non-spastics. The mean hematocrit of mild spastics (N=73) was 51.2%.

The findings suggested that intracranial hemorrhage might be the immediate cause of spastic diplegia of prematurity.

Serial No. NDS (CF)-68 PR/PN 1634

This paper was presented at the Annual Meeting of the American Academy for Cerebral Palsy at the Americana Hotel in Miami Beach, Florida, December 10-14, 1968.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-68 PR/PN 1635
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neuropsychologic Deficits in Children of Diabetic Mothers.

Previous Serial Number: Same

Principal Investigators: John A. Churchill, M.D., PRB, NINDS
Heinz W. Berendes, M.D., PRB, NINDS
Jean Nemore, R.N., B.A., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.20
Professional:	.10
Other:	.10

Project Description:

Pregnancy appears to intensify diabetes, and in some women the disease can be detected only when gravid. The ill effect of maternal diabetes mellitus on the outcome of pregnancy has been known in terms of high rates of fetal losses, neonatal deaths and congenital malformations. Whether intellectual deficits are associated with maternal diabetes remains uncertain.

This study is addressed to the question whether the neurologic and psychologic status of children born to diabetic mothers differs from that of children of non-diabetic women. In addition, the question is posed whether an effect, if found, could be attributed to diabetes directly or to a complication of the disease, such as acidosis or prematurity. Particular attention was directed toward the occurrence of acetonuria, since previous studies have shown that perinatal mortality is exceedingly high when diabetic acidosis occurs. Other studies have indicated that perinatal mortality is similar in both latent and florid diabetic states. Therefore, the neuropsychologic status of children born to mothers with mild and with severe diabetes was studied separately.

Cases for study were drawn from the Perinatal Study of the National Institute of Neurological Diseases and Stroke, the total number being about 50,000 pregnancies. The study population included only pregnancies resulting in single, liveborn babies who had been given the Bayley mental and motor examination at eight months, or the Binet test at four years of age.

Patients who had diabetes were classified in accordance with the system of White. For the purpose of the present study, mothers who had Class A diabetes, including cases with abnormal glucose tolerance curve and gestation diabetes, were grouped separately from those who had diabetes of Classes B, C, D, E, and F (hitherto referred to as Class B+).

In addition to keto-acidosis of a degree considered to be clinically significant, the presence of acetonuria alone was noted. Diabetics were classified into Groups I, II and III depending upon whether acetonuria (or diacetic acid) were present, absent, or not determined, respectively.

Each diabetic case was matched for hospital of birth, race and sex with a single non-diabetic case. "Controls" were matched also for the exact or next lowest socioeconomic index value, the same or greater maternal age, and the same or nearest birth order.

Dependent variables studied were: a) Duration of pregnancy, b) Birthweight, c) Bayley mental and motor exams given at 8 months of age, d) The Binet I.Q. test given at 4 years of age, e) a rating scale for postural control observed at one year of age.

237 cases of maternal diabetes were studied.

The offspring of diabetic mothers differed significantly from matched non-diabetics in the Bayley mental and motor scores given at 8 months, the posturing rating scale observed at 12 months of age, and the Binet I.Q. administered at 4 years of age. Duration of pregnancy was significantly shorter in diabetics than in controls. Birthweight of diabetics, while greater, did not differ significantly from controls.

The frequency of other neurologic abnormalities was approximately equal in the diabetic and control groups.

Acetone positive diabetic cases showed significantly greater developmental deficits than their matched controls. Again, in the diabetics, duration of pregnancy was significantly shorter and birthweight was not significantly different than controls. Acetone negative diabetic cases did not differ from their controls in the neuropsychologic measures. Duration of pregnancy was shorter than controls, as was the case in acetonuric diabetics. However, birthweight of acetone negative diabetics was greater than their controls: $p < .05$.

Sacral defects, most of which were dimples and pilonidal sinuses were observed in a higher proportion of insulin-treated than untreated cases, the difference in frequency of cases in the groups being statistically significant; $P < .01$. The frequency of sacral defects in offspring of diabetic mothers given no insulin differed little from that of the non-diabetic "control" cases.

In conclusion, maternal diabetes mellitus during gestation was found to have an adverse effect on neuropsychologic attributes of children. Deficits were

observed in the Bayley Scale measured at 8 months of age, posturing factors derived from neurologic examination given at 12 months of age, persisting to affect the Binet I.Q. at 4 years of age. Of singular importance was the finding that diabetes accompanied by acetonuria was associated with the adverse effects on the fetus, but no deficits were found in the offspring of diabetic mothers free of acetonuria.

This paper was presented on March 14, 1968 at a weekly seminar at the University of Washington Medical School, Seattle, Washington.

Honors and Awards: None

Publications: Churchill, J.A., Berendes, H.W., and Nemore, J.: Neuropsychologic Deficits in Children of Diabetic Mothers. Amer. J. Obstet. Gynec. In press.

Serial No. NDS (CF)-68 PR/PN 1637
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Relationship of Maternal Biliary Disease to IQ of the Offspring

Previous Serial Number: Same

Principal Investigators: John A. Churchill, M.D., PRB, NINDS
Heinz W. Berendes, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.04
Professional:	.02
Other:	.02

Project Description:

In a previous study, the investigators had demonstrated significantly lower I.Q.'s of the children whose mothers had gall bladder disease when compared to a control group whose mothers did not have gall bladder disease. This study was designed for the purpose of confirming these findings with PRB data.

A listing was obtained of all cases indexed "Abdominal Operation" where the child had been given the 4-Year Psychological Examination. Out of this group, there were 98 cases of definite gall bladder disease. Six were second study pregnancies. One child was mongoloid, so the case was discarded. One child had focal motor epilepsy and was excluded; and one could not be matched for a control (this case also had diabetes). In each one of the cases, the presence of cholecystectomy was ascertained. There were 54 white patients with well-verified gall bladder disease; 3 problematic (2 had pancreatitis and 1 was a very peculiar case in that one couldn't be sure that she had gall bladder disease. She had had encephalitis, meningitis, was legally blind, had had an appendectomy, an episode of so-called gall bladder disease with cholecystectomy, sensitivity to sunlight in the form of a rash); 26 cases were Negro, 3 cases Puerto Rican. The cases were matched for institution, race, sex, S-E Index, maternal age, and birth order. Two controls had to be disqualified and others chosen because one child had congenital heart disease, another focal cerebral seizures.

The mean difference in I.Q. between the cases and their controls was 9 points, $p<.002$. Excluding the pancreatitis cases, the probability level was less than .001. The Negro group was not statistically significant in I.Q. difference.

Among the six women with gall bladder disease who had a first and second study pregnancy, the 2nd child had a lower I.Q. in each case. The mean difference was 6.8; $p<.01$. This suggests that duration of the disease may have a bearing upon the problem.

Maternal age and parity tend to be higher for those with lower I.Q.'s. The S-E Index was not significantly different.

One interesting observation was that the mothers with Italian heritage had higher I.Q. children than the others. An explanation is that the Italian mother, who has gall bladder disease, may get along fine because she uses a great deal of olive oil which is high in linoleic acid. Fish are also very high in linoleic acid.

The study is still in progress.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/PN 1638
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Relationships of Maternal Amino Acid Blood Levels to Fetal Development

Previous Serial Number: Same

Principal Investigators: John A. Churchill, M.D., PRB, NINDS
Kamran S. Moghissi, M.D., F.A.C.O.G., Wayne State University, Detroit, Michigan
Charles Frohman, Ph.D., Lafayette Clinic, Detroit, Michigan
T. N. Evans, M.D., F.A.C.O.G., Wayne State University, Detroit, Michigan

Other Investigators: None

Cooperating Units: Wayne State University, Detroit, Michigan
Lafayette Clinic, Detroit, Michigan

Man Years:

Total:	.05
Professional:	.04
Other:	.01

Project Description: The hypothesis of this study is that blood amino-acid concentrations of gravida in the last trimester is positively correlated with birthweight, length and cranial volume of the baby. The study, now including well over 100 cases, supports the hypothesis. Correlation coefficients on this data are being run and will be available for review. Presented at meeting of American College of Obstetrics and Gynecology April 28, 1969, Bal Habor, Florida.

No association between dietary data and amino-acid levels or of infant measures could be found. Children are being given Bayley Scales at 8 months of age, but too few tests have been completed.

Chromatographic analysis of individual amino acids are being done. Twelve analyses have been done, the results of which look too good to mention yet. The next phase of the study will be to see if amino acid levels can be elevated by giving protein concentrates and if so whether the infant measures increase.

Honors and awards: None

Publications: Churchill, J.A., Moghissi, K.S., Frohman, C., and Evans, T.N.: Relationships of maternal amino acid blood levels to fetal development. Amer. J. Obstet. Gynec. In press.

Serial No. NDS (CF)-68 PR/PN 1639
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Gestational Acetonuria and Some Developmental Measures in the Offspring.

Previous Serial Number: Same

Previous Title: Neuropsychologic Deficits in Children Whose Mothers Had Episodes of Acetonuria.

Principal Investigators: John A. Churchill, M.D., PRB, NINDS
Heinz W. Berendes, M.D., PRB, NINDS
Lee Willerman, PhD., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.30
Professional:	.20
Other:	.10

Project Description: Previously, it was found that the IQ of offspring of acetonuric diabetic mothers was lower than the IQ of children whose diabetic mothers were free of acetonuria. The question then is whether the presence of acetonuria in the mother was associated with deficits in intellectual function.

Two-hundred and ten cases were found where the mother had acetonuria on one or more prenatal visits and where the child had had the Binet IQ test. The cases were matched with controls by institution of birth, race, sex, S.E. Index, maternal age, and parity. Of the 210 cases, 111 cases were mothers with acetonuria in the third trimester. This group of 111 offspring had a mean Binet IQ of 89.0 and their matched controls had a mean Binet IQ score of 97.6-t=5.05, p value significant less than .001 level. The other 99 mothers had acetonuria before the third trimester. This group of 99 offspring had a mean Binet IQ score of 92.8 and their matched controls had a mean Binet IQ score of 96.1-t=2.09, p value significant at .05 level.

This paper was presented at the American Public Health Association Meeting at Detroit, Michigan, November 1968.

Study has been completed and manuscript is ready for submission to a journal for publication.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1735
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Failure of Maternal Weight Gain, A Comparison of Outcomes of Infants Whose Mothers Failed to Gain More than Ten Pounds During Pregnancy to those Gaining 25 to 35 Pounds.

Previous Serial Number: None

Principal Investigator: John A. Churchill, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.2
Professional:	.1
Other:	.1

Project Description: From data printed out, we have not been able to demonstrate an association between maternal weight gain and Bayley developmental scores or 4-year I.Q. An apparent difference in birthweight disappeared when weight gain was made proportional to maternal weight, and where short gestations were removed from the study.

One would think a priori that maternal weight gain ought to be coupled with nutritional impairment, thus influencing outcome in the child. Furthermore, other studies have shown such associations. This data requires more searching review for hidden problems.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1736
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Twin Study

Previous Serial Number: None

Principal Investigators: Lee Willerman, Ph.D., PRB, NINDS
John A. Churchill, M.D., PRB, NINDS
Zekin A. Shakhashiri, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.2
Professional:	.2
Other:	.0

Project Description: Twins have lower birthweights and IQ than singletons. Study confirms the hypothesis, and has progressed to the stage of final analysis for publication. The thesis is that the human mother often cannot adequately supply nutrients to two fetuses.

Within the study, we have also tried to confirm our previous findings that the smaller of identical twins has the lower IQ. In this we failed. The reason appears to lie in use of the 4-Year IQ as the outcome measure. We found the correlation coefficient, r, of IQ within identical twin pairs was 0.7. This value is not characteristic of other findings of 0.9. Variance of the smaller twin was also excessively great for reasons we cannot at the moment explain.

Honors and Awards: None

Publications: None

Serial No. NIH (CP)-69 PR/PN 1737
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Amino Acid Assays on PRB Frozen Serum Samples

Previous Serial Number: None

Principal Investigators: John A. Churchill, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.2
Professional:	.1
Other:	.1

Project Description: Amino acid determinations on frozen PRB samples on cases with outcomes already known. This series of studies has been planned. The first study, which is aimed at relating individual amino acid concentrations in sera of cases and controls included in the acetonuria study, has been approved by the NINDS Directorate.

If the utility of frozen PRB sera for this purpose can be established, an enormous potential for use of the sera in association with other PRB data will be made available.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1738
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Consideration of Etiological Factors in Spastic Diplegia of Prematurity

Previous Serial Number: None

Principal Investigators: John A. Churchill, M.D., PRB, NINDS
Jack H. Carleton, M.D., PRB, NINDS
Heinz W. Berendes, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.2
Professional:	.1
Other:	.1

Project Description: This work is an extension of the previous work to include other presumptive etiologies. Among findings are: spastic diplegia occurs in true prematures and not in small-for-dates babies; low hematocrit from hemolytic anemia is not associated with diplegia; spastic diplegia occurs in Cesarean-sectioned gravida where the reason for section is not relevant to treatening situation for the child.

This paper was presented at the Annual Meeting of the American Academy of Cerebral Palsy at the Americana Hotel in Miami Beach, Florida, December 10-14, 1968.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1739
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Cerebral Hemorrhage in Premature Infants.

Previous Serial Number: None

Principal Investigators: Jack Carleton, M.D., PRB, NINDS
John A. Churchill, M.D., PRB, NINDS
Heinz Berendes, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.3
Professional:	.2
Other:	.1

Project Description: Brain specimens were available in 25 cases where the infant was premature, weighing less than 2.0 Kg.; had weight and hematocrit measurements; but died before leaving the hospital.

The brains were examined for the presence of gross intracerebral hemorrhage; 16 cases with cerebral hemorrhage being found. Hemorrhage was present in 12 out of 15 cases that had lost more than 10% of body weight in the postnatal period. Of 10 cases losing less than 10% of the birthweight, 4 had intracranial hemorrhage ($X^2 = 4.2$; p .05).

Hematocrits were less than 55% in 12 out of 13 cases with intracerebral hemorrhage, but in 12 cases with hematocrits above 55%, only 4 had hemorrhage. ($X^2 = 9.4$; p .002).

The findings of depressed postnatal weights and hematocrits in premature infants who had intracerebral hemorrhage were those which were also observed in surviving prematures with spastic diplegia.

The analogy between prematures perishing with intracerebral hemorrhage on one hand, and surviving to have spastic diplegia on the other, in respect to postnatal weight loss and depressed hematocrit suggests that intracerebral hemorrhage is the immediate cause of this species of cerebral palsy.

This paper was presented at the Annual Meeting of the American Academy for Cerebral Palsy at the Americana Hotel in Miami Beach, Florida, December 10-14,

1968.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1740
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Predictive Value of Early Signs in Low Birthweight Infants

Previous Serial Number: None

Principal Investigators: Joseph S. Drage, M.D., PRB, NINDS
Karin B. Nelson, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.20
Professional:	.10
Other:	.10

Project Description: A group of 1,364 single, liveborn infants with birthweights ranging from 1000 to 2000 grams has been studied regarding outcome during the first year of life. Specific neurological signs during the nursery period have been related to the neurological status at 1 year of age and death during the first year of age. A positive early sign was defined as occurrence on at least one of the four first examinations of the specific sign being studied. Signs studied included: cry, suck, palmar grasp, moro reflex, muscle tone, and 5-minute Apgar score of 4 or less.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1741
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Apgar Scores as They Relate to Performance on the 4-Year Psychological Examinations

Previous Serial Number: None

Principal Investigator: Joseph S. Drage, M.D., PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.20
Professional:	.10
Other:	.10

Project Description:

The objective of this study is to test the hypotheses that low Apgar scores are associated with increased incidence of low test performance on the 4-year psychological examination; testing, specifically, the Binet IQ score, raw scores on the Graham Block Sort, and the clinical impression regarding fine motor development, gross motor development, behavioral profile, and the overall impression on the entire test battery. Controls for the study were birthweight above and below 2500 grams, education of the gravida, race, and sex. Tabulations were originally obtained based on approximately 10,000 4-year psychological examinations. There were significant relationships at .01 to .001 for white infants weighing less than 2500 grams for the overall impression between low and high 5-minute scores, and for white infants of over 2500 grams for fine motor development in the overall assessment of the behavior. For white infants over 2500 grams, the relationship between low and high scores to overall impression of the child was significant at p .001. For Negro infants of less than 2500 grams, there was a significant relationship between the low and high Apgar scores for fine motor, gross motor at a level of $p < .001$, and for the behavioral profile and overall impression at a p of .01 to .001. Relationships between the high and low score group for 4-year IQ and the Graham Block Sort scores, controlled on

maternal education, suggested findings but were not conclusive. It then became apparent that the cohort had become available on approximately 24,000 children with an update of the data file and this study has now been rerun and is in the process of analysis. It is hoped that by doubling the sample some of the relations which were borderline would be shortened considerably and a more precise relationship can be demonstrated.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1742
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Effect of Rapid Succession of Pregnancy on the Neuropsychological Development of the Offspring

Previous Serial Number: None

Principal Investigators: W. Lawrence Holley, M.D., PRB, NINDS
Arthur L. Rosenbaum, M. D., PRB, NINDS
John A. Churchill, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.45
Professional:	.40
Other:	.05

Project Description: The objective of the study was to determine the effect of short inter-pregnancy interval on the child as measured by birthweight, pregnancy duration, and psychological measures.

All children conceived within 3 months and born within 12 months of a previous full-term pregnancy were matched with children born after an interval of 2-5 years. The groups were matched for race, sex, place of birth, socioeconomic status, maternal age, and parity. The two groups were compared for differences in birthweight, pregnancy duration, Bayley developmental scores at 8 months of age, Binet IQ at 4 years of age, and a neurological evaluation at 1 year of age. The results were analyzed using a t-test for paired groups and results were evaluated on a 2-tail analysis.

The children born within the short inter-sibling interval had significantly lower birthweight, lower scores on the Bayley Scales of Mental and Motor Development at eight months of age, lower scores on the Revised Stanford-Binet IQ at 4 years of age, and more neurologically suspicious or abnormal children at 1 year of age.

The differences noted suggest that rapid succession of pregnancy is damaging to the child. The work adds emphasis to the need for family planning. The work may also reflect a nutritional deficit pre-natally and possibly in the early postnatal years which would contribute to neuropsychological effects.

Honors and awards: None

Publications:
Presented at meeting of Society for Research in Child Development, March 26-29, 1969, Santa Monica, California.

Serial No. (CF)-69 PR/PN 1743
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neuropsychologic Outcome of Child Born Via the Breech Position Compared with Children Born Via the Occiput Anterior Position

Previous Serial Number: None

Principal Investigator: Arthur L. Rosenbaum, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.20
Professional:	.15
Other:	.05

Project Description: This study was designed to determine whether children born via the breech position have greater neuropsychological impairments than those born either left occiput anterior (LOA) or right occiput anterior (ROA).

All breech cases born into one of the institutions participating in the Collaborative Perinatal Research Project who weighed more than 2.5 kg. and for whom a 4-year IQ score was available (N-62), were compared to the LOA and ROA populations utilized by Willerman and Churchill in their study on fetal head position (reported elsewhere in this volume). The methodology employed for data analysis was identical to that utilized in the preceeding study on the occiput posterior position.

Tables I and II show that the Breech offspring had significantly lower 1-minute Apgar and Bayley Mental scores than both LOA and ROA offspring. However, there were no significant differences between the two groups in duration of pregnancy, birthweight, Bayley moter scores or Binet IQ scores.

The LOA group showed a significantly higher incidence of extensor plantar responses at one year than the Breech cases, 25.3% and 4.8% respectively. There were no significant differences between the groups with respect to delayed postural control or history of seizures.

This study was presented at conference on "Physical Trauma as an Etiological Agent in Mental Retardation" Lincoln, Nebraska, October 13-16, 1968.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1744
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neuropsychologic Outcome of Children Whose Mothers Were Anemic During Pregnancy

Previous Serial Number: None

Principal Investigators: Lawrence E. Gershon, M.D., PRB, NINDS
John A. Churchill, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.25
Professional:	.20
Other:	.05

Project Description: While anemia during pregnancy is most commonly caused by a shortage of iron, it was believed that this may correlate with other nutrition inadequancies and thus may be used as an indicator of general nutriental inadequacies. Do these inadequacies have any long term effect on the child?

Approximately 100 cases of severe anemia (women with hematocrits less than 25) were selected and matched to controls on the basis of institution, race, sex, and socioeconomic index. The subject and control groups could not be distinguished on the basis of gestational age, Bayley motor score, Bayley mental score, or Binet IQ. The birthweight of the subject differed significantly from that of control with the p of .01. This we attribute to greater parity of the subject group. The study is now being written.

Honors and awards: None

Publications: None

Serial No. NDS. (CF)-69 PR/PN 1745
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Effect of Prepartum Hemorrhage with or without Treatment with Estrogen or Progesteron on the Neuropsychologic Outcome of the Offspring

Previous Serial Number: None

Principal Investigators: Lawrence E. Gershon, M.D., PRB, NINDS
Arthur L. Rosenbaum, M.D., PRB, NINDS
John A. Churchill, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.32
Professional:	.30
Other:	.02

Project Description: Prepartum maternal hemorrhage has long been suspected to adversely affect fetal outcome. One investigator has reported a 20% incidence of maternal hemorrhage in a group of malformed children. The possibility that estrogen and progesteron administration prevents these hazards has been investigated but results are inconclusive. This project is designed to study the following hypothesis: 1) Maternal prepartum bleeding affects adversely neuropsychological outcome of the offspring; 2) Treatment with sex steroids for bleeding during pregnancy affects this outcome.

Method of procedure: 1. Patients with a history of prepartum bleeding, not treated with steroids, to be matched with patients without prepartum bleeding and who did not receive steroids. 2. Patients with a history of bleeding prepartum, who have received steroids, matched to cases who did not bleed prepartum but who received steroids. 3. Patients with a history of prepartum bleeding treated and not treated with estrogens. 4. Patients with no history of prepartum bleeding treated and not treated with progesterons. 5. Patients with a history of prepartum bleeding treated and not treated with estrogen. 6. Patients with no history of prepartum bleeding treated and not treated with estrogens. These groups will then be prepared in relation to the following outcome variables: Birthweight, Bayley mental and Bayley Motor scores given at 8 months of age, Binet IQ test given at 4 years of age.

The cases and controls will be computer matched. At present, we are awaiting computer printout of the cases. The study is still in progress.

Honors and awards: None

Publications: None

Serial No. NDS(CF)-69 PR/PN 1746
1. Perinatal Research Branch, NINDS
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neuropsychologic Outcome of Children Whose Mothers Were Given Chloromycetin

Previous Serial Number: None

Principal Investigators: Lawrence E. Gershon, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.35
Professional:	.30
Other:	.05

Project Description: Hypothesis: gravida receiving antibiotics in last trimester of pregnancy have offspring that test higher in IQ than non-tested controls. Altering bacterial flora with antibiotics may permit better amino acid absorption in the gut.

The study has been completed but not reported because of uncertainties. The number of chloromycetin cases was rather small.

No differences could be found between the subject and control cases on the following measures: Birthweight, Bayley mental and motor scores, and Binet IQ given at 4 years of age.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1747
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neuropsychologic Outcome of Children Whose Mothers Were Treated with Penicillin During Pregnancy

Previous Serial Number: None

Principal Investigators: Lawrence E. Gershon, M.D., PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.17
Professional:	.15
Other:	.02

Project Description: It was hypothesized that penicillin may reduce the bacterial interference in utilization of amino acid required for fetal development. A case listing of all those women reported to have received penicillin for at least 8 weeks was requested. The cases were hand-reviewed and matched for controls by institution, race, sex, and socioeconomic index.

No differences could be found between the subject and control cases on the following measures: Birthweight, Bayley mental and motor scores, and Binet IQ given at 4 years of age.

Penicillin may differ because cases used were those on the drug over many months' time, mothers being treated for rheumatic fever. In this time, bacterial flora may have become stabilized.

Honors and awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1748
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neonatal Polycythemia: I. A Manifestation of Chronic Injury During Distress.

Previous Serial Number: None

Principal Investigator: Miles M. Weinberger, M.D., PRB, NINDS

Other Investigators: Arthur Oleinick, M.D., EPID, NCI
John A. Churchill, M.D., PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.75
Professional:	.50
Other:	.25

Project Description:

The objectives of the study were to study demographic and maternal factors associated with neonatal polycythemia.

As part of the protocol during the Collaborative Study on Cerebral Palsy, capillary hematocrits were obtained as near to 48 hours as possible (generally between 36 and 60 hours) on 44,683 newborns, or 86% of all 77 and over was identified, and controls, matched for institution and year of birth, race, sex, socioeconomic index, and presence or absence of 4-year follow-up examination were selected randomly from all infants with 48-hour hematocrits 50 through 65. Various demographic and maternal factors were identified on both subjects and controls, and differences were statistically evaluated.

The subject cases (those with polycythemia manifested by hematocrits 77 and over) were found to have been the product of longer gestation, but were smaller in weight than the control population. There was an increase in incidence of placental pathology and the placenta of the subject cases was significantly lighter than the weights of the controls. One-minute and five-minute Apgar scores were both lower in the subject cases and there was a greater incidence of dysmaturity diagnosed in the subject cases. When compared with the whole Collaborative Study population, infants with polycythemia were noted to come from lower socioeconomic groups. Data suggest that neonatal polycythemia may be a manifestation of chronic intrauterine distress.

Data is now being analyzed. This analysis is expected to be complete and a full report of this data should be available at least in first draft form in preparation for submission for publication within the next two months.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1749
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Neonatal Polycythemia: II. Outcome.

Previous Serial Number: None

Principal Investigators: Miles M. Weinberger, M.D., PRB, NINDS
John A. Churchill, M.D., PRB, NINDS

Other Investigators: Arthur Oleinick, M.D., EPID, NCI

Cooperating Units: None

Man Years:

Total:	.75
Professional:	.50
Other:	.25

Project Description:

The objectives of the study were to determine polycythemia in the neonatal period as an adverse effect on neuropsychological outcome.

See project report on Neonatal Polycythemia: I. A Manifestation of Chronic Injury During Distress covering demographic and maternal factors. In addition, the neuropsychological status of these infants was examined at various intervals through four years of age.

Examining only the outcome of those infants without recognized congenital malformation and gestational ages of 36 weeks and greater, it was found that while these infants tended to be small for gestation age and have lower Apgar scores, there was no significant difference in other findings in the newborn period. There was also no difference in psychological scores at eight months. At one year, there was no difference in abnormal neurological findings between subjects and control cases. At four years, however, the subjects did manifest a statistically-significant lower score on the 4-year Stanford-Binet examinations than the controls. This difference was greatest among Negroes, especially among the Negro females. White males did not manifest any difference in 4-year IQ.

Significance is not so much that some differences in 4-year IQ were found among some of the subgroups of the polycythemic infants, but that contrary to the expectations from the literature the differences between polycythemic infants and non-polycythemic controls were so small.

Final analysis and a first draft of a report of this data should be ready within the next two months and eventual submission to the pediatric literature.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1750
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Abnormal Hematopoiesis in Newborns with Down's Dyndrome.

Previous Serial Number: None

Principal Investigators: Miles M. Weinberger, M.D., PRB, NINDS
Arthur Oleinick, M.D., EPID, NCI

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.75
Professional:	.50
Other:	.25

Project Description:

The objectives of the study were to describe and attempt to evaluate the possible significance of an unusual relationship found between neonatal polycythemia and Down's syndrome.

Utilizing data in the Collaborative Study on Cerebral Palsy, it was found that hematocrits performed at 48 hours of age were available on 44,683 newborns. The top percentile, hematocrits 77 and over, were identified and congenital malformations along with other information variables were ascertained in all subjects and a group of matching controls selected from all infants with hematocrits 50 through 65. This range of hematocrits constituted the 15th through the 85th percentile.

9 of the 61 known liveborn infants with Down's syndrome in the Collaborative Study population were found among the 418 with hematocrits of 77 and over. No cases of Down's syndrome were found among the nearly-equal size group of control infants.

The association of congenital myeloproliferative disorders with Down's syndrome has been recognized since as early as 1954. There is also some substantiation from the literature that there may also be abnormal proliferation of other bone marrow elements. The undescribed relationship between Down's syndrome and neonatal polycythemia demonstrates that the abnormal bone marrow proliferative disorder described in the literature in newborns with Down's syndrome is truly a generalized marrow disorder and not limited to the white cell

elements alone.

Data collection is complete and is now in the process of being prepared for submission to Lancet for publication.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/PN 1751
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Congenital Rubella Presenting as Retarded Language Development.

Previous Serial Number: None

Principal Investigators: Miles M. Weinberger, M.D., PRB, NINDS
Mary Wootton Masland, MA., Montgomery County Health Department
Ruth Alice Asbed, M.D., M.P.H., Montgomery County Health Department
John L. Sever, M.D., Ph.D., PRB, NINDS

Other Investigators: None

Cooperating Units: Montgomery County Health Department
Easter Seal Treatment Center

Man Years:

Total:	1.00
Professional:	.75
Other:	.25

Project Description:

The objectives of the study were to determine the incidence of previously undetected congenital rubella among pre-school children with retarded language development.

A pre-school communications screening program was conducted in Montgomery County, Maryland. Advertisements through news media, local nursery schools, daycare centers and local physicians urged parents to bring children suspected of speech, hearing or visual disorders of any etiology for examination. No specific request was made for children suspected of congenital rubella as a cause of such defects. Blood specimens were obtained from most of the children examined and rubella hemagglutination inhibition antibody determinations were performed on the sera.

From the 52 children born in 1964, the year of the last rubella epidemic, 41 sera were obtained. Rubella antibody was found in 5 children and 4 of these were found upon further examination to have clinical signs consistent with congenital rubella infection. This diagnosis had not been previously made in three of these four children.

The findings suggest that many children damaged by congenital rubella during the 1964 epidemic may yet be unknown to the medical and educational community. Identification of these children may be possible using the combined clinical and serological approach described.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/BS 1640
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The relationship of demographic, perinatal and other developmental characteristics to intellectual and motor performance of pre-school children.

Previous Serial Number: NDS-(CF)-68 PR/BS 1640

Principal Investigator: Sarah H. Sleigo, Ph.D., PRB, NINDS

Other Investigators: Jaswant Khanna, Ph.D., University of Tennessee
Joseph Weber, formerly Office of Biometry, NINDS

Cooperating Units: University of Tennessee
Office of Biometry, NINDS

Man Years:

Total:	.20
Professional:	.20
Other:	.00

Project Description:

30 characteristics of some 13,000 study children have been related to their pass-fail performance on individual items in the psychology battery administered at four years of age. Preliminary analyses relating four demographic variables to performance on the Stanford-Binet show that : (I) differences among white, Negro and Puerto Rican children in IQ, socioeconomic index, educational level of mother and proportion of males to females are highly significant. Whites exceed the other two groups in mean IQ and socioeconomic index. Differences among the groups in mean number of years of mother's education are more evenly spaced with whites > Negroes > Puerto-Ricans. Sex ratios in these groups follow a different order with Puerto-Ricans > whites > Negroes; (II) Highly significant differences in percent pass by ethnic group occur on all 28 of the Stanford Binet items examined. These items cover the test levels from II years 6 months through VI years. Among whites percent pass is significantly higher than among the total group on 27 items. Among Negroes percent pass is significantly lower than the total group on 26 items. Among Puerto-Ricans, percent pass is significantly lower than the total group on 16 items, does not differ from the total group on nine items and is higher on three items; (III) Within both the white and Negro groups, children who pass have a significantly higher socioeconomic index than those who fail on all of the 28 Binet items. Among Puerto-Ricans however these differences occur on only 10 items; (IV) Similarly, among both whites and Negroes, educational level of mother is significantly higher for passers than for those who fail on all 28 items. However for Puerto Ricans this occurs on only five items; (V) Among whites, sex

differences in performance occur on 13 of the 28 Binet items with proportionally more males than females failing these items. Among Negroes sex differences in favor of females occur on 15 items and in favor of males on one item. Among Puerto Ricans sex differences are significant on only five items, again with more males than females failing these items.

The content of the items on which all of the above differences occur is of course highly relevent and is now being categorized.

Subsequent analyses will explore the relationship of perinatal, neurological and other psychological variables to performance at four years of age.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/BS 1641
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1,1968 through June 30, 1969

Project Title: Fetal Head Position and Intelligence

Previous Serial Number: Same

Principal Investigator: Dr. Lee Willerman, PRB, NINDS

Other Investigator: Dr. John A. Churchill, PRB, NINDS

Cooperating Unit: Section on Pediatric Neurology, PRB, NINDS

Man Years:

Total:	.30
Professional:	.25
Other:	.05

Project Description:

Objectives: From hospital records at Boston Lying-in, head position during birth and whether forceps were applied during delivery was determined for 213 children who had been given the WISC at seven years of age and the Stanford-Binet IQ test at four. The results indicated that children whose occiputs were situated in the right anterior quadrant of the maternal pelvis during delivery (ROAs) had significantly lower Stanford-Binet IQs than Ss whose occiputs were situated in the left anterior quadrant of the maternal pelvis (LOAs). This relationship was observed despite the application of forceps. The implications of these findings are discussed in terms of presumptive perinatal trauma and psychological functioning.

Willerman, Lee, Relationship of fetal head position during delivery to intelligence, In press, Physical trauma as an etiological agent in mental retardation, 1968.

Honors and Awards: None

Publications: Churchill, J. A., Willerman, L., Grisell, J., Ayers, M. A., Effect of head position at birth on WISC Verbal and Performance IQ, Psychol. Rep. 23: 495-498, 1967.

Serial No. NDS (CF)-68 PR/BS 1642
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Maternal Pelvic Size and Intelligence

Previous Serial Number: Same

Principal Investigator: Dr. Lee Willerman, PRB,NINDS

Other Investigators: Dr. J. A. Churchill, PRB, NINDS
Dr. A. Rosenbaum, PRB,NINDS

Cooperating Unit: Section on Pediatric Neurology, PRB, NINDS

Man Years:

Total:	.30
Professional:	.25
Other:	.05

Project Description:

Objectives: The purpose of this project is to explore possible relationships between clinical obstetric estimations of maternal pelvic inadequacy and intellectual impairment in the offspring.
Stanford-Binet IQs of 287 vertex births whose mothers were coded as having upon clinical examination, either borderline or contracted pelves, were compared on IQ to a sample of 243 children whose mothers had adequate pelves. The finding indicated that women coded as having borderline or contracted pelvic outlets, as compared to those coded as adequate, had children with significantly more frequent low IQs ($IQ \leq 85$). Clinical estimates of inadequate pelvic inlet or mid pelvis regions were not associated with significantly more frequent low IQs.

This study has been completed and was presented at the Fourth Multidisciplinary Conference on the Etiology of Mental Retardation, Lincoln, Nebraska, October 13-16, 1968.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/BS 1643
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Bayley Scores, 4-Year Intelligence and Socioeconomic Index

Previous Serial Number: Same

Principal Investigator: Dr. Lee Willerman, PRB, NINDS

Other Investigators: Dr. Sarah H. Sledge, PRB, NINDS
Dr. Miriam Fiedler

Cooperating Unit: Children's Hospital Medical Center of Boston

Man Years:

Total:	.40
Professional:	.35
Other:	.05

Project Description:

Objectives: The purpose of this project is to describe the fate of developmentally retarded and advanced children as measured by the Bayley Scale of Infant Development. This study involves the Bayley scores of approximately 3000 white children. Analysis indicates that the four-year IQ of the children in the lowest quartiles on the Mental and Motor Scales administered at eight months of age depends strongly on the socioeconomic class of the child. The higher the socioeconomic status, the less impaired the child. In contrast, in children scoring in the upper quartiles on both the Bayley Mental and Motor Scales, there is little association between socioeconomic status and IQ. Other findings are that children in the lowest Bayley Motor quartile have significantly lower IQ when compared to those in the upper quartile.

A report was presented at the Biennial Meetings of the Society for Research in Child Development, Santa Monica, California, March 25-29. The manuscript has been completed and is currently undergoing NIH review before submission for publication.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/BS 1644
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Maternal Pelvic Size and Neurological Outcome

Previous Project Title: Maternal Pelvic Size and Neurological Outcome at Seven Years

Previous Serial Number: Same

Principal Investigator: Dr. Lee Willerman, PRB, NINDS

Other Investigator: Dr. J. A. Churchill, PRB, NINDS

Cooperating Unit: Section on Pediatric Neurology, PRB, NINDS

Man Years:

Total:	.20
Professional:	.15
Other:	.05

Project Description:

Objectives: The purpose of this project has been to explore the relationship of small maternal pelvic size to neuropsychological outcome in the child. This study was based on a sample of 213 vertex births. As part of the Collaborative Perinatal Research Project, these children had received psychological examinations at four and seven years of age.

Major Findings: The results indicated that children born of small pelvis mothers, as compared to children born of large pelvis mothers, had significantly lower Stanford-Binet IQs. Children born of these small pelvis mothers who had been delivered by forceps made more errors on the Tactile Finger Recognition Test at seven years of age than those children of large pelvis mothers who were delivered by forceps. Study completed.

Willerman, Lee. Maternal pelvic size and neuropsychological outcome, presented at the Fourth Multidisciplinary Conference on the Etiology of Mental Retardation, Lincoln, Nebraska, October 13-16, 1968.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/BS 1752
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Duration of Membrane Rupture and Psychological Outcome

Previous Serial Number: None

Principal Investigator: Dr. Lee Willerman, PRB, NINDS

Other Investigators: Dr. Arthur L. Rosenbaum, PRB, NINDS
Dr. John A. Churchill, PRB, NINDS

Cooperating Unit: Section on Pediatric Neurology, PRB, NINDS

Man Years:

Total:	.20
Professional:	.15
Other:	.05

Project Description:

Objectives: Previous research by others has suggested that during labor the head of the fetus in vertex delivery is subjected to far greater mechanical pressure after membrane rupture than before. We are currently awaiting a print-out of infant developmental measures and IQ scores as a function of interval between membrane rupture and birth.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/BS 1753
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Growth and Intellectual Development of Children From Consanguineous Matings

Previous Serial Number: None

Principal Investigator: Dr. Lee Willerman, PRB, NINDS

Other Investigators: Dr. Ntinos C. Myrianthopoulos, PRB, NINDS
Dr. Alfred F. Naylor, PRB, NINDS

Cooperating Unit: Section on Epidemiology and Genetics, PRB, NINDS

Man Years:

Total:	.35
Professional:	.30
Other:	.05

Project Description:

Objectives: Consanguineous matings have been reported to be associated with a higher incidence of fetal and neonatal mortality as well as mental retardation in the offspring. The present study will examine outcomes in the offspring of 148 sets of parents in the Collaborative Study who are second cousins or closer. The hospital records of these cases have now been identified and are currently being abstracted.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/BS 1754
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Growth and Intellectual Development of Children From Interracial Matings

Previous Serial Number: None

Principal Investigator: Dr. Lee Willerman, PRB, NINDS

Other Investigators: Dr. Alfred F. Naylor, PRB, NINDS
Dr. Ntinos C. Myrianthopoulos, PRB, NINDS
Dr. John A. Churchill, PRB, NINDS

Cooperating Units: Section on Epidemiology and Genetics, PRB, NINDS
Section on Pediatric Neurology, PRB, NINDS

Man Years:

Total:	.50
Professional:	.40
Other:	.10

Project Description:

Objectives: Offspring from Negro-white matings (n=171) were individually matched to children from white-white and Negro-Negro matings on hospital of birth, socioeconomic index, and marital status. Though not significantly different from the controls in either length or weight at birth, by four months of age the interracials were significantly smaller than the controls. At one year the interracials were still smaller, but the magnitude of the differences had diminished considerably. On psychological test performance at eight months, no differences were observed. At four years the IQs of the interracial children were significantly lower than the white controls, but not significantly lower than the Negro controls. Birthweights and lengths of the interracial children were intermediate to the larger white and smaller Negro children regardless of the race of the interracial mother. These results suggest a genetic basis to the findings that Negro children weigh less and are shorter than white children at birth.

A manuscript has been prepared for publication and is currently undergoing NIH review before submission to a journal.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/BS 1755
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: A Directory of Control Cases for Selected Outcome Variables

Previous Serial Number: None

Principal Investigator: Dr. Lee Willerman, PRB, NINDS

Other Investigator: None

Cooperating Unit: None

Man Years:

Total:	.15
Professional:	.10
Other:	.05

Project Description:

Objectives: Many study proposals emanating from PRB staff follow a familiar design. Index cases are matched with controls on, at least, four variables, Race, Sex, Institution, and SEI. Less frequently cases are matched on parity, birthweight or gestational age as well.

The Directory of Controls is designed to be applicable for studies of this type. The control Directory is divided into two parts. The first part provides means, n's, standard deviations and variance for all possible crosses of Race, Sex, Institution, and SEI (by five point intervals) for selected outcome variables. The second part of the Directory lists the NINDS numbers as well as the outcome variables for the cases falling into each cell.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/BS 1756
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Preschool Stuttering and Early Maternal Attitudes

Previous Serial Number: None

Principal Investigator: Raymond H. Holden, Ed.D., Visiting Scientist
PRB, NINDS
Paul J. LaBenz, Sc.D., PRB, NINDS

Cooperating Unit: Child Development Study, Brown University

Man Years:

Total:	.35
Professional:	.30
Other:	.05

Project Description:

The etiology of stuttering is not clearly defined, and many theories compete for primacy of explanation. Psychoanalytic literature has indicated the cause of stuttering to be a conflict between the desire to speak and the desire not to speak. It is considered a neurotic disorder in which personality disturbance is reflected in disturbance of speech. Glauber (1958) refined the earlier psychoanalytic positions of Freud, Brill and Coriat in proposing that stuttering will be more easily reversible in early childhood as a result of the improvement in the total family constellation but particularly by influencing maternal attitudes toward the child.

This study evaluates the relationship of children dysfluent in speech at age three, and earlier attitudes of their mothers as reported on the Parental Attitude Research Instrument (PARI) obtained when the child was eight months old. A randomly selected group of children matched for age, sex and race but with no dysfluent behavior will serve as controls.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/BS 1757
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Social Class and Outcome in the Neurologically Abnormal Infant

Previous Serial Number: None

Principal Investigator: Raymond H. Holden, Ed.D., Visiting Scientist, PRB, NINDS

Other Investigator: Lee Willerman, Ph.D., PRB, NINDS

Cooperating Unit: None

Man Years:

Total:	.30
Professional:	.20
Other:	.10

Project Description:

The hypothesis to be tested is that the magnitude of the difference in four year IQ between children of high socioeconomic status and low socioeconomic status will be significantly greater among abnormal infants than their matched controls.

Previous studies in cerebral palsy (Solomons, Holden, and Denhoff, 1963; Paine, 1962) have shown changes towards more normal functioning by age three in some cases, in children definitely diagnosed as neurologically impaired during the first year of life. Reasons for such improvements have not been clearly delineated.

Recent work has also suggested greater vulnerability of the retarded infants to the adverse affects of their environment (Willerman, Sledge and Fiedler, 1969). A more rigorous test of the validity of this hypothesis would be to study infants who have both a definite diagnosis of a specific neurological condition as well as abnormally low developmental test scores during infancy. The present study attempts to assess the effects of SES as a possible influence on the outcome of neurologically and psychologically impaired infants.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/BS 1758
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Maturity at birth, mental and motor performance at eight months and intelligence quotient at four years.

Previous Serial Number: None

Principal Investigator: Sarah H. Sledge, Ph.D., PRB, NINDS

Other Investigators: Jerome Deutschberger, Office of Biometry, NINDS
H. W. Berendes, M.D., PRB, NINDS
Mary Dowling, Office of Biometry, NINDS

Cooperating Unit: Office of Biometry, NINDS

Man Years:

Total:	.20
Professional:	.20
Other:	.00

Project Description:

Objectives of the study are to determine the relationship of birthweight and gestational age to (1) mental and motor development at eight months as measured by the Bayley Scales and (2) IQ as measured at four years of age. Preliminary investigation has shown a direct relationship between the above measures of maturity at birth and performance at eight months. (Mendelson et al unpublished). This study will investigate the stability of the relationship over time.

The cohort consists of all liveborn whites and Negroes excluding multiple births. The independent variables are birthweight, gestational age and birthweight and gestational age taken together. The dependent variables are the eight month mental and motor scores and the four year IQ. The control variables are ethnic group, sex and educational level of mother. Preliminary findings indicate the following: (I) When controlled for education of mother, ethnic group and sex, four-year IQ increases with birthweight; (II) Similarly, when controlled for the above mentioned factors, four-year IQ increases with length of gestation. This relationship is not as strong as the one with birthweight; (III) When controlled for birthweight and gestation and ethnic group and sex, four-year IQ increases with educational level of mother. This relationship appears to be slightly more pronounced among whites than among Negroes; (IV) Four-year IQ increases as eight month mental and motor scores increase when controlled by ethnic group, sex and education of mother. This

relationship is stronger with the mental than with the motor scores.

Analyses of these data are still in progress .

Honors and Awards: None

Publications: None

Serial No. NDS (CH-63 PR/EG 1173
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: A Study of Socioeconomic, Medical and Genetic Factors in Major Congenital Malformations

Previous Serial Number: Same

Principal Investigator: Dr. N. C. Myrianthopoulos, PRB, NINDS

Other Investigators: Dr. C. Chung, School of Public Health, University of Hawaii
Alice Baszynski, PRB, NINDS
Dr. Luz Froehlich, PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.15
Professional:	.15
Other:	.00

Project Description:

Objectives: This is a continuation of a project to study the relation of medical and genetic factors to major congenital malformations. The results of the first phase have already been published (Amer. J. Hum. Genet. 20:44-60, 1968).

Proposed course: In the second phase the plan is to utilize the complete cohort of the Collaborative Study to investigate especially those relationships which have been shown to be significant in the preliminary study. In addition a number of rare major congenital malformations are being studied. These include absence of abdominal muscles, agenesis of diaphragm, Poland's syndrome, congenital dislocation of the hip, microphthalmia and imperforate anus. These were obtained for singletons and twins from the Ped-8 and Ped-12. Pedigrees have been constructed and the pathological material is being reviewed.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-63 PR/EG 1174
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Birthweight in Relation to Selected Socioeconomic Variables

Previous Serial Number: Same

Principal Investigator: Dr. N. C. Myrianthopoulos, PRB, NINDS

Other Investigators: Dr. Joshua Lederberg, Stanford University

Cooperating Units: None

Man Years:

Total:	.10
Professional:	.05
Other:	.05

Project Description:

Objectives: This is a continuation of a study to relate birthweight to socioeconomic and medical variables. The results of the first part of the study have already been published (Ann. Hum. Genet. 31:71-83, 1967).

Proposed course: In the second part the plan is to compare children in the 100th percentile of birthweight with children in the 50th percentile of birthweight and children of diabetic mothers, in terms of several socio-economic, biological and medical variables. A magnetic tape with all the necessary data has been prepared. Analysis is done at Stanford University under Dr. Lederberg's direction.

Honors and Awards: None

Publications: None

Serial No. NIS (CF)-63 PR/EG 1175
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Determination of the Zygosity of Twins Born to Mothers in the Collaborative Study

Previous Serial Number: Same

Project Coordinator: Dr. N. C. Myrianthopoulos, PRB, NINDS

Cooperating Units: All Institutions participating in the Collaborative Study

Man Years:

Total:	.15
Professional:	.15
Other:	.00

Project Description:

Objectives: This is a continuing project to determine the zygosity and epidemiologic characteristics of twins born to Study mothers.

Methods employed: Twin zygosity is determined by comparison of sex, placentation, blood groups, and finger and palm prints. This information is forwarded by all Institutions to the Section on Epidemiology and Genetics where it is classified and analyzed by special methods.

Major findings: In all, 615 pairs of twins have been identified. Among white twins 34.6% were MZ and 65.4% DZ; among Negro twins 28.8% were MZ and 71.2% DZ. The frequency of DZ twinning increases to age 35, then falls sharply. The frequency of MZ twinning is steady to age 35, then increases for both whites and Negroes. There is an increase in frequency of twinning in higher socioeconomic groups.

Proposed course: To study all twins in terms of a variety of genetic and socioeconomic variables. A paper entitled "A Survey of Twins in a Large, Experimental Population" was presented in October 1968 at the American Society of Human Genetics, Austin, Texas.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-63 PR/EG 1177
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Genetic and Socioeconomic Factors in Early and Late Fetal Death

Previous Serial Number: Same

Principal Investigator: Dr. N. C. Myrianthopoulos, PRB, NINDS

Other Investigators: Esther Jackson, Office of Biometry, NINDS

Cooperating Units: None

Man Years:

Total:	.15
Professional:	.15
Other:	.00

Project Description:

Objectives: To determine what effect do genetic and socioeconomic factors have on pregnancy wastage and if a distinction can be made etiologically between early and late fetal deaths.

Methodology and major findings: Discriminant analysis of 1,877 early and late fetal deaths with respect to 40 medical, genetic and socioeconomic variables, shows that toxemia, anemia and complications of pregnancy are good discriminants in both whites and Negroes; prior pregnancies and prior pregnancy wastage in whites only; and socioeconomic status in Negroes only. Knowledge of sex of study child improves the power of the discriminant function.

Proposed course: Another run is now being made to identify the least number of variables which would give good discrimination.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-63 PR/EG 1184
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Population Dynamics of Tay-Sachs Disease and Other Sphingolipidoses

Previous Serial Number: Same

Principal Investigator: Dr. N. C. Myrianthopoulos, PRB, NINDS

Other Investigators: Dr. Stanley Aronson, State University of New York

Cooperating Units: State University of New York

Man Years:

Total:	.15
Professional:	.15
Other:	.00

Project Description:

Objectives: This is a continuation of a study to determine whether differential fertility favoring the Jewish heterozygote can account for the 100-fold higher frequency of Tay-Sachs disease and the gene responsible for it among the Jewish compared with non-Jewish population in the U. S. Evidence for selective advantage of the heterozygote was found in the first part of the study (Amer. J. Hum. Genet. 18:313-327, 1966).

Proposed course: The plan in the second part is to investigate whether or not such advantage can be demonstrated in other sphingolipidoses, to study the demography of these disorders and to determine whether resistance to tuberculosis or some other infectious disease confers a selective advantage to the heterozygote.

Methodology: About 4,000 cases of Jewish immigrant patients who had TB have been collected from the records of the American Chronic Disease Center, Denver, Colorado. The distribution of places of origin of these patients is now being compared with that of ancestors of Tay-Sachs and Niemann-Pick children, and that of a large number of selected controls.

Honors and Awards: None

Publications: Myrianthopoulos, N. C. and Aronson, S. M.: A genetic and demographic study of Niemann-Pick disease. Proc. XII Int. Congr. Genet. 1:307, Tokyo, 1968.

Serial No. NDS (CF)-65 PR/EG 1274
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Genetic Bases of Neonatal Reflexes

Previous Serial Number: Same

Principal Investigator: Dr. A. F. Naylor, PRB, NINDS

Other Investigators: Dr. N. C. Myrianthopoulos, PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.14
Professional:	.10
Other:	.04

Project Description:

Objectives: To investigate the validity of regarding the suck, rooting and other neonatal reflexes as genetic entities.

Major Findings: An initial set of cases retrieved for absence of one or more of these reflexes was reviewed and seemed to have high frequencies of various kinds of trauma whose base line frequencies were unknown.

Proposed Course: To place limits on the frequencies of losses of suck, rooting, palmar grasp, plantar grasp and Moro reflexes because of mutation or segregation at gene loci specifically affecting manifestation of these reflexes.

Specifications have been written for new data processing which will yield estimates of frequencies of specific reflex absences within a population to be regarded as healthy on grounds other than specific reflex deficit.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-65 PR/EG 1275
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Study of Family Size with Respect to Rh Blood Type and Other Variables

Previous Serial Number: Same

Principal Investigator: Dr. A. F. Naylor, PRB, NINDS

Other Investigators: Dr. N. C. Myrianthopoulos, PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.02
Professional:	.02
Other:	.00

Project Description:

Objectives: The project will re-examine the suggestion made by Glass in 1950 that fetal loss in Rh negative women may actually be over-compensated for in a population practicing birth control, which may be lifted when incompatibility loss occurs. Information on the Rh type of gravidae, previous incompatibility complications, family planning practices and race will be related to age-corrected family sizes of gravidae.

This project has been largely inactive.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-65 PR/EG 1276
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Sequential Aspects of Occurrence of Spontaneous Abortion in Family Histories

Previous Serial Number: Same

Principal Investigator: Dr. A. F. Naylor, PRB, NINDS

Other Investigators: Dr. Dorothy Warburton, College of Physicians and Surgeons of Columbia University

Cooperating Units: None

Man Years

Total:	.40
Professional:	.30
Other:	.10

Project Description:

Objectives: To relate the risk of spontaneous abortion to maternal age and prior reproductive experience. A special point under investigation is whether apparent age effects are explicable by a tendency for intrinsic habitual aborters to remain in the reproductive population longer in attempts to compensate for unsuccessful pregnancies. Also conditional risks are to be estimated. A first round of analyses has been performed.

Proposed Course: Revision of computer programs has been decided upon to exploit in full long reproductive histories which were previously omitted because information content was imperfect, although often very high. Utilization of these cases requires adjustments of programs to handle unknown gestation periods, unknown dates of events, occurrence of multiple births and substitution of repeat pregnancy data for missing first study pregnancy OB-2 information. This has been done.

An existing manuscript is being partially rewritten and a new one is being drafted in collaboration with Dr. Warburton.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-67 PR/EG 1510
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Study of Maternal Effects in the Production of Congenital Malformations

Previous Serial Number: Same

Principal Investigator: Dr. N. C. Myrianthopoulos, PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.10
Professional:	.10
Other:	.00

Project Description:

Objectives: To determine the extent to which maternal factors are involved in the production of congenital malformations, and to single out those malformations and conditions of the newborn in which the role of maternal factors, genetic and environmental, appears to be deciding.

Methods Employed: The GEN 9-8 was used to obtain a history of outcome of prior pregnancies, in families in which half-siblings are present. Study pregnancies were also included.

Major Findings: In all, 152 cases were identified and these were screened for occurrence of congenital malformations and other conditions among children by different fathers. Six conditions were found to occur in high frequency among half sibs: Rh trouble, convulsions, congenital heart disease, club foot, mental retardation and polydactyly. In a large number of half sibships different conditions and malformations were also observed. These are now being analyzed.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-67 PR/EG 1511
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: A Comparative Study of Reporting of Various Congenital Malformations

Previous Serial Number: Same

Principal Investigators: Dr. N. C. Myrianthopoulos, PRB, NINDS
Sylvia Hay, Dental Health Center, PHS, San Francisco, California

Other Investigators: None

Cooperating Units: Congenital Anomalies Section, Epidemiology Branch, Dental Health Center, PHS, San Francisco, California

Man Years:

Total:	.10
Professional:	.10
Other:	.00

Project Description:

Objectives: To assess the quality of the reporting of cleft lip and palate as well as other congenital malformations on birth certificates.

Major Findings: A review of birth certificates of children with clefts born in the Collaborative Study from 1962 to 1965 showed that only 46.4 percent contained information about the clefts and none contained information about a specific defect, cleft gum. Six children with cleft gum from the Medical College of Virginia have been examined for persistence of the clefts in childhood, and x-rays were taken to determine whether a bone abnormality underlies the anomaly of the soft tissue. These have been interpreted as showing some abnormalities. Experts at NIDR suggested that a special study be conducted, preferably at Freedmens Hospital to determine the frequency of this condition at birth and assess its clinical significance.

Proposed Course: Plans for such a study are uncertain.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-67 PR/EG 1512
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Relationship of Maternal ABO and Rh Blood Groups to Pregnancy Outcome and Infant Survival

Previous Serial Number: Same

Principal Investigators: Dr. N. C. Myrianthopoulos, PRB, NINDS
Dr. Bernice H. Cohen, Johns Hopkins University
Jeffrey E. Sayre, Johns Hopkins University

Other Investigators: None

Cooperating Units: Department of Chronic Diseases, The Johns Hopkins University School of Hygiene and Public Health

Man Years:

Total:	.05
Professional:	.05
Other:	.00

Project Description:

Objectives: This is a Collaborative Study with the Johns Hopkins School of Hygiene and Public Health to examine the role of ABO and Rh Blood groups in the risk of fetal, neonatal and infant mortality, to investigate blood group associations other than incompatibility and to determine any difference by ethnic, socioeconomic and maternal variables.

Methodology: Computer output was obtained with information concerning gravidae and study children (including fetal deaths) of the 1959-64 cohort, consisting of obstetric and reproductive history, laboratory data, gestational age, sex of offspring, birthweight, ABO and Rh types and socio-economic index scores.

Current Status: The study has been temporarily interrupted because of Mr. Sayre's departure from Johns Hopkins before the data could be developed. Dr. Cohen, however, is anxious to carry the project through and it is anticipated that progress will be made in the near future.

Honors and Awards: None

Publications: None

Serial No. NIDS (CF)-67 PR/EG 1513
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: A Genetic Study of Congenital Polycystic Kidney

Previous Serial Number: Same

Principal Investigator: Dr. N. C. Myrianthopoulos, PRB, NINDS

Other Investigator: None

Cooperating Units: None

Man Years:

Total:	.05
Professional:	.05
Other:	.00

Project Description:

Objectives: To study the formal genetics of congenital polycystic kidney and to clarify the relationship of this fatal malformation with the unilateral polycystic kidney of the adult which is compatible with life.

Major findings: Thirty-four children who died of pathologically verified congenital polycystic kidney have been identified. This gives a birth incidence of about 1 in 1,650 births. The frequency of this malformation appears to be significantly higher in Negro than in White babies. Family histories have been reviewed and extensive pedigrees have been constructed.

Proposed course: The pathological material is now being reviewed before segregation analysis is made.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-67 PR/EG 1514
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Record Linkage of Relatives Registered in the Collaborative Study

Previous Serial Number: Same

Principal Investigator: Dr. A. F. Naylor, PRB, NINDS

Other Investigators: Dr. N. C. Myrianthopoulos, PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.10
Professional:	.05
Other:	.05

Project Description:

Objectives: To identify all relatives of gravidae registered in the Collaborative Study.

Methodology: A preliminary run before the recent Master File update netted 6,500 highly reliable reports of relatives of gravidae in the study. The virtual closing of the GEN-5 file makes appropriate and opportune the creation of a record linkage system. Consequently specifications are being submitted for data processing to do the following:

(A) create a cross-reference file based on the explicit GEN-5 information;

(B) obtain a rough estimate of the frequency of underreporting of relatives when one of potentially linkable babies dies early or is lost to the Study;

(C) estimate overreporting when one of a pair of linkable babies has a conspicuous morbidity.

(D) investigate the practicality and value of uncovering unreported linkages by use of gravidas' maiden names, places of birth, etc.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-67 PR/EG 1515
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Rh Hemolytic Disease in Negro and White Infants

Previous Serial Number: Same

Principal Investigator: Dr. A. F. Naylor, PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.00
Professional:	.00
Other:	.00

Project Description:

Objectives: To confirm a report that high Rh antibody levels have smaller morbid effects in Negro than in White babies, although this is not true for ABO antibodies.

Major findings: Preliminary and indirect confirmation has been obtained, from a small data sample under study in this Section, for reports in the literature that high Rh antibody titers are not as highly associated with serious morbidity in Negroes as in whites.

Proposed course: Further data processing aids to move this study forward seem justified and have been requested.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-67 PR/EG 1516
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Size of Placenta in Relation to Mother-Fetus Antigenic Difference

Previous Serial Number: Same

Principal Investigators: Dr. Dorothy Warburton, College of Physicians and Surgeons of Columbia University
Dr. A. F. Naylor, PRB, NINDS

Other Investigators: Dr. Toshio Fujikura, PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.90
Professional:	.60
Other:	.30

Project Description:

Objectives: To investigate the hypothesis published by Billington in 1964, that sensitization of the mother during pregnancy against paternal antigens leads to non-pathological placental hypertrophy and increased birthweight in succeeding pregnancies.

Major findings: Analysis of a large sample of study data has given convincing support to the hypothesis. A manuscript is being drafted reporting the nature and variety of the evidence.

Proposed course: Arrangements for consequent laboratory studies to obtain the most direct evidence possible have successfully been negotiated and will soon be implemented.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/EG 1645
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Detailed Evaluation and Comparative Study of the Puerto Rican Cohort in the Collaborative Study

Previous Serial Number: Same

Principal Investigators: Dr. Glen S. Bartlett, PRB, NINDS

Other Investigator: Dr. N. C. Myrianthopoulos, PRB, NINDS

Cooperating Units: None

Man Years:

Total:	.15
Professional:	.10
Other:	.05

Project Description:

Objectives: To investigate and define the characteristics of the Puerto Rican Cohort in three Collaborative Study Institutions, Columbia, New York Medical, and Pennsylvania Hospitals, and to compare the cohort with the white and Negro cohorts at the same institutions.

Methodology: Emphasis is on socioeconomic background, fertility, assimilation and acculturation, and the biological variables which seem to be influenced by these factors. The study is considering separately the mother, the infant, and the family into which the child is born. The present phase of the study is exploratory rather than hypothesis-testing, and is limited to the first year of the child's life.

Current Status: Initial data have been tabulated and analysis is underway. Additional data will be available shortly.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/EG 1646
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Study of the Physical Growth of Children in the Collaborative Study

Previous Serial Number: Same

Principal Investigator: Dr. Glen S. Bartlett, PRB, NINDS

Other Investigators: Dr. Pearl Fisher, Office of Biometry, NINDS

Cooperating Units: Office of Biometry, NINDS

Man Years:

Total:	.20
Professional:	.20
Other:	.00

Project Description:

Objectives: To develop growth curves on Collaborative Study children using two mathematical approaches.

Methods Employed: The first, partially completed, uses percentile distributions of measurements at various ages to plot growth curves. The second, now underway is evaluating the growth of the children individually and collectively using a variety of cure-fitting techniques, to develop growth rates at different points in time as well as growth curves from computed measurements. The two methods will be compared for comparability of the resulting curves.

Preliminary Findings: Initial evaluation of data on weight and length of the study children from birth through four years indicates that growth rates are accelerated over standards currently in use, especially during the first year of life and beyond age 2 years. This acceleration is present for boys and girls and for whites and non-whites. Boys are heavier and longer than girls through age 4 years; whites are heavier and longer than non-whites through about age 3, after which non-whites begin to exceed whites in length. These data are being submitted to detailed computer analysis by curve-fitting techniques.

Proposed Course: The present phase of the study is aimed at population description and is limited to race and sex breakdowns; future phases will evaluate comparative growth of other subgroups of the population such as premature infants and infants with certain neurologic diseases. Curves are being developed on infants from birth through 7 years.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/EG 1647
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Development and Evaluation of an Index of Reproductive Performance for the Purpose of Identifying High Risk Pregnancy Suspects

Previous Serial Number: Same

Principal Investigator: Dr. Glen S. Bartlett, PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.00
Professional:	.00
Other:	.00

Project Description:

Objectives: To develop a mathematical index of reproductive performance based on prior pregnancy wastage -- fetal and infant mortality and morbidity -- for the purpose of identifying the so-called "high risk" pregnancy suspect.

Methodology: The predictive value of the index will be tested by applying it to future pregnancy performance (first and subsequent study pregnancies). The relationship of the index to socioeconomic parameters known to be related to poor reproductive performance will also be investigated.

The study has been inactive during the past year but a request for computer handling of the data is being prepared.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/EG 1648
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Further Investigation of the Socioeconomic Index as a Descriptive and Predictive Instrument

Previous Serial Number: Same

Principal Investigators: Dr. Glen S. Bartlett, PRB, NINDS
Dr. N. C. Myrianthopoulos, PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.00
Professional:	.00
Other:	.00

Project Description:

Objectives: The socioeconomic status score or socioeconomic index, developed by the Bureau of the Census for use with the 1960 Census, has been used with good results in this Section to describe the Collaborative Study population, and by others to describe other populations. This study is designed to explore mathematically the three component parts of the index -- education and occupation of the head of household, and family income -- in order to assess their relative contributions to the index; to evaluate the ability of the index to encompass other socioeconomic variables not used in deriving the index; and to investigate whether or not the index, in addition to being descriptive, can also be used as a reliable predictive instrument.

Methodology: Linear discriminant function and multiple regression analysis will be used to determine appropriate weights to be applied to the component factors, and correlation coefficients will be obtained between the index and its components, and external variables.

Proposed Course: The present phase is based on information obtained when the gravida registered for her first study pregnancy; later phases will compare gravidae at subsequent study pregnancies and at the 7-year follow-up interview.

The study has been inactive during the past year but a request for computer handling of the data is being prepared.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/EG 1759
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Genetic Significance of Congenital Abnormalities in the Sibs and Other Relatives of Children with Cerebral Palsy

Previous Serial Number: None

Principal Investigators: Dr. Valerie A. Cowie, PRB, NINDS
Dr. N. C. Myrianthopoulos, PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	0.10
Professional:	0.10
Other:	0.00

Project Description:

Objectives: To investigate the likelihood that some cases of cerebral palsy are determined by a recessive gene, and that this gene may be responsible for other deleterious effects besides cerebral palsy, manifest in the affected individual and/or his sibs.

Methodology: All cases of cerebral palsy in the study are being examined for congenital abnormalities in the index case and congenital abnormalities and cerebral palsy in the sibs. Other family data relating to congenital abnormalities, cerebral palsy and consanguinity are being collected. Segregation and other types of analysis will be used.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/EG 1760
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Congenital Anomalies in Sibs of Mongols

Previous Serial Number: None

Principal Investigator: Dr. Valerie A. Cowie, PRB, NINDS
Dr. N. C. Myrianthopoulos, PRB, NINDS

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.10
Professional:	.10
Other:	.00

Project Description:

Objectives: To investigate the hypothesis that a possible underlying genetical predisposition beyond the cytogenetical level may produce other congenital abnormalities in addition to mongolism in the sibs, and possibly other relatives, of mongols.

Methodology: At this stage the search for congenital abnormalities is limited to the sibship of the mongol. Information relating to the sibships of all mongols in the study is obtained from the GEN. 5-8 and is verified from hospital and physicians records.

Work is in progress.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/EG 1761
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Sex-Chromatin Screening of a Training School and Subsequent Investigation of Patients with X-Chromosome Anomalies

Previous Serial Number: None

Principal Investigator: Dr. Valerie A. Cowie, PRB, NINDS
Dr. N. C. Myrianthopoulos, PRB, NINDS

Other Investigators: Dr. Al Aish, National Institute of Child Health and Human Development
Dr. Sarah H. Sledge, PRB, NINDS
Dr. Benedict Nagler, Lynchburg Training School and Hospital, Lynchburg, Virginia
Dr. Michael J. Rostafinski, Lynchburg Training School and Hospital, Lynchburg, Virginia
Dr. David Rosenthal, Laboratory of Psychology, NIMH
Dr. T. P. Zahn, Laboratory of Psychology, NIMH
Dr. M. Buchsbaum, Laboratory of Psychology, NIMH

Cooperating Units: National Institute of Child Health and Human Development, NIH, Bethesda, Md., Lynchburg Training School and Hospital, Lynchburg, Virginia, National Institute of Mental Health, Bethesda, Md.

Man Years:

Total:	0.10
Professional:	0.10
Other:	0.00

Project Description:

Objectives: To explore further the existence and nature of an organic constitutional basis for psychological abnormalities in subjects with X-chromosome anomalies, of sufficiently high intelligence to cooperate, using a battery of psychological tests and psychophysiological tests.

Methodology: The first step is to find subjects by screening, using the buccal smear method. Permission has now been obtained through the courtesy

of the Superintendent, Dr. Nagler, and Dr. Rostafinski, to screen patients at Lynchburg Training School, Virginia. Subjects found by screening to have anomalies involving the X-chromosome will be studied further by investigation of the full karyotype from peripheral blood culture.

Work is in progress.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/EG 1762
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Investigation of Parental Reaction to the Realization of Handicap in a Child

Previous Serial Number: None

Principal Investigator: Dr. Valerie Cowie, PRB, NINDS

Other Investigators: None

Cooperating Units: Department of Neurology, Children's Hospital of the D. C.

Man Years:

Total:	0.10
Professional:	0.10
Other:	0.00

Project Description:

Objectives: To ascertain by interview the reaction of parents to the impact of realization that their child is mentally and/or physically handicapped, and their later adjustment to the situation. In this way, it is hoped to gain insight that will be useful in parental counselling in various categories of conditions, genetically determined or exogenous in origin, with a wide variety of prognostic implications.

Methods employed: The procedure involves interviews with parents of patients who have been diagnosed by physicians in the Department of Neurology, Children's Hospital of the D. C. (through whose courtesy the patients are referred). A psychiatric evaluation is made of their reactions, and subjective psychiatric assessment is backed by the objective measure of the Eysenck Personality Inventory, a scale which is widely used and has been found to be a useful single tool for the measurement of two basic dimensions of personality, neuroticism and extraversion.

This work is in progress, with excellent cooperation from the parents participating.

Honors and Awards: None

Publications: None

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Biologic Pattern Data Processing

Previous Serial Number: Same and incorporating Serial No. NDS (CF)-66 PR/P 1354

Principal Investigators: Lewis E. Lipkin, M. D.
Russell A. Kirsch

Other Investigators: Philip G. Stein
Howard M. Shapiro, M. D.
Peter F. Lemkin

Cooperating Units: Artificial Intelligence Group
National Bureau of Standards

Office of Associate Scientific Director
Clinical Trials
National Cancer Institute

Man Years

Total: 8.0
Professional: 4.8
Others: 3.2

Project Description:

The accomplishments this year may be divided into the categories of construction of a scanner-microspectrophotometer system; further development of the LISP-PAX system; and miscellaneous tasks.

1. Scanner-Microspectrophotometer Subsystem: A scanner-microspectrophotometer subsystem for the LINC-8 computer has been constructed and is presently in partial operation. This instrument allows light transmission measurements to be made from slides which are positioned automatically with a high precision. The various scanning parameters, all of which are under direct computer control are as follows:

   A. X-Y Stage Position: Stepping motor controls were built to enable the computer to position the stage to within a precision of about 0.6 microns over a useful range of 2.5 cm. This enables coarse control of image position to be under computer control.

B. Scanner Position: Within the field obtained by the coarse position control, the galvanometer mirror scanner can measure transmitted light in any one of 256 x 256 positions arranged in a rectangular array which subtends about one percent of the area of a full field as viewed with a standard eyepiece. Each position of the scanner head is directed by computer control and is reproducible to within less than one scanner position.

The transmitted light measurement made is compared by analog circuits with values obtained from a reference beam to compensate for variations in flux from the light source and for voltage variations. To accomplish this, a new reference beam with quartz light pipe feeding its own photomultiplier was constructed as was the necessary log-ratio differential amplifier circuitry. It was also necessary to make optical changes in the scanner head to make its image parfocal with that of the visually observed image. Changes were also made in the microspectrophotometer head to accommodate a photomultiplier tube which matched that of the reference beam.

C. Fine Focus: A stepping motor was attached to the fine focus control to enable the computer to control z-position of the microscope to a precision of approximately 0.2 microns. Thus, the x, y, and z resolutions of the system are all of comparable value.

D. Illumination Color and Bandwidth: Stepping motors also control the monochromator light source to enable the computer to select among 13,000 prism positions in the usable spectrum of the xenon arc source and, for each one, to control the width of the masking slit in the monochromator. The design for these and the other stepping motors was done by NBS with the construction and LINC-8 programming being done by NINDS.

Since the number of binary digits of information obtainable from a tissue section 2.5 cm. x 2.5 cm. x 30 microns is of the order of 10^{14} bits, it is of course out of the question to scan and record a whole slide at maximum resolution; but, for partial recording of images, a magnetic tape is of use. To provide this capability, a nine-track magnetic tape drive and its controller was constructed by NBS. Programs written by NCI make this tape acceptable to the PDP-10 computer at DCRT. Some more general interfacing circuitry for the LINC-8 to use the above tape drive and other future input - output devices were designed by NBS and constructed by NINDS.

II. Further Development of the LISP-PAX System: The LISP-PAX image processing system constructed by NBS on the Q-32 computer at System Development Corporation in California has been providing a very powerful tool for developing methods for processing images. It has been the main tool used for our image processing research and has also provided a basis for the design of a more powerful such system currently under construction on the PDP-10 computer by the image processing staff at DCRT.

During the past year, several additions were made to the basic LISP-PAX system. One such addition enables edges of regions within images to be determined by the computer based on a kind of spatial differentiation. Another set of improvements enable Boolean operations and shifting operations to be done on gray scale images rather than just on binary (black and white) images.

Beyond these additions to the basic LISP-PAX, many programs were written to solve specific problems. These include:

A. A magnetic tape input conversion routine to accommodate the format of the NBS (Moore) picture scanner.

B. A simulator for the programmable scanner which uses tape motion to simulate the motion of a slide under the microscope. This makes possible experiments in registration of images which ordinarily are not located at positions in a slide corresponding to convenient computer partitions of the slide.

C. A complete blob analyzer for single gray scale image "windows" of size 36 x 36 resolution elements. This analyzer decomposes an image into disjoint "blobs" by level slicing the gray scale window and then for each blob finds:

   1. Its location in the window.

   2. The size of the blob.

   3. A density histogram of the points of the blob.

   4. A histogram of the directions of tangents to its perimeter.

D. A form of general solution to the image segmentation problem. This program takes a quantized gray scale window of an image and partitions the image into disjoint regions which are bounded by density gradients. It then varies the density gradient criterion to generate other partitions. The results are presented as list structures giving an articular analysis of the regions and the inclusion relations between the regions. It appears that this method of segmenting images is both more natural and more economical of machine capacity than the usual method of rectangular raster decomposition.

E. A program for display of the articular analysis of images obtained with the general segmentation program. This program was used for the analysis of several single neuron images and for an image take from a more complex tissue section photograph. In each case, all the morphologically significant components of the images appeared as proper components in the resulting analysis.

F. A program for accepting paper tape from the LINC-8. This is to be used for processing programmable scanner output on the Q-32 until the completion of the PDP-10 image processing system and its connection to the scanner.

G. A program for obtaining serial section reconstructions of optically sectioned images. This program removes from single optical sections part of the images component due to adjacent sections and then provides successive serial sections in outline or cartoon form. A technique for mounting these successive sections on transparencies was used to reconstruct a whole neuron from optical serial sections.

III. Miscellaneous Tasks: Several miscellaneous activities during this period were peripherally related to the above main tasks:

A. A picture syntax seminar was conducted primarily for the members of the DCRT image processing group to develop acquaintance with syntactical techniques for processing images.

B. Some incidental or experimental use was made of time sharing facilities on the following computers: SDS-940 (Dial-Data Inc.), IBM-7090 (CTSS-Project MAC, Massachusetts Institute of Technology), Univac-1108 (University of Maryland, DEC PDP-6 (Stanford University).

C. Assistance was provided to NINDS in developing laboratory facilities for electronic testing and construction, small machine shop construction, and photographic processing.

D. Use of the LISP-PAX system was provided to a few outside users for brief experimental use.

E. High speed Teletype equipment (Model 37) was obtained and used with the PDP-10. This equipment functioned well and provided useful additional capabilities for upper and lower case typing as well as various non-printing control functions.

In FY 1968 there was a Project Report for "Automated Microspectrophotometry Employing the LINC Computer," Serial No. NDS (CF)-66 PR/P 1354. It was incorporated during FY 1969 with Serial No. NDS (CF)-65 PR/P 1278.

Honors and Awards: None

Publications: None

Serial No. NDS (CF-66)PR/P 1342
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Length of the Umbilical Cord

Previous Serial Number: Same

Principal Investigators: Toshio Fujikura, M. D.
Luz A. Froehlich, M. D.
Lewis E. Lipkin, M. D.

Other Investigators: None

Cooperating Units: All Collaborating Institutions

Man Years
Total: 0.04
Professional: 0.04
Others: 0

Project Description:

To determine if there is a relative correspondence between cord length and the two main indices of embryonic growth, namely birth weight and gestational age.

The cohorts in the study were single birth core cases where the total length of the umbilical cord was available in the Ped 1 form (Examination of the Neonate). Only infants with birth weights of 1,001 grams and over and gestational ages of 28 to 43 weeks were included. For birth weight - cord length associations, a total of 8,696 whites and 9,290 Negroes were available for analysis and for gestational age-cord length relationships, 4,869 whites and 6,434 Negroes were analyzed.

Mean cord lengths showed a progressive increase in both white and Negro with increments of gestational age and birth weight. Percentage distribution on cord lengths also showed a gradual shift from the shorter to the longer cord with increasing gestation and birth weight.

The mean cord length in the Negro was usually less than its white counterpart, the difference being constant at about 1.4 cm at each gestation interval.

One disturbing discovery in this study was the institutional difference in reporting of cord lengths which could not be explained on the basis of population differences. There were also inter-examiner differences in reporting of the same segments of cord. Although the average inter-examiner difference was about 2 cm, differences up to 10 cm were randomly noted.

This is not to say that cord length is a non-usable parameter, but it should be used cautiously. We feel it can be used in study case-matched control types of investigation, the controls being matched for institution, race, birth weight or gestational age, and birthdate.

The project has been discontinued.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-66 PR/P 1352
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Neuropathological Study of a Series of Selected Monkey Brains from Animals in the Perinatal Period

Previous Serial Number: Same

Principal Investigator: Jack H. Carleton, M. D.

Other Investigators: Lewis E. Lipkin, M. D.

Cooperating Units: Bionetics Research Laboratory, Inc.

Man Years

Total: .05
Professional: .00
Others: .05

Project Description:

Objectives: This study was initiated to evaluate as a comparison to the Perinatal Research Project material the brains of the primate perinatal period according to the protocol established for the processing of whole brains coming from the Collaborative Study. Data on the prenatal period, delivery, neonatal care, developmental aspects, and circumstances of death in these cases has been collected and will be considered after the neuropathological findings have been described.

Methods Employed: The specimens for study have been processed according to Project methods including whole and sectioned brain photography, and Project staining procedures. A microscopic examination protocol has been devised so that all brains can be compared in tabular form.

Major Findings: All 103 brains in the series have been processed and classified as to age, species and quality of histological preparation. Ages range from stillbirth to 2½ years for the three major species which will be evaluated. The detailed protocol for describing the neuropathological observations has not been completed since our major effort has been to process all Project specimens to the paraffin embedded stage and then proceed with histological evaluations.

Significance to Bio-medical Research and the Program of the Institute: It is anticipated that this study will enhance our understanding of perinatal neuropathology and serve as a laboratory control for evaluation of technical procedures used in the Project's protocol.

Proposed Course: Continue to completion as research efforts and correlations of human and primate perinatal neuropathology are warranted.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-66 PR/P 1353
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: A Sequential Study of Ultrastructural Changes in an Experimentally Produced Traumatic Brain Lesion

Previous Serial Number: Same

Principal Investigator: Jack H. Carleton, M. D.

Other Investigators: John L. Priester

Cooperating Units: None

Man Years

Total: .15
Professional: .05
Others: .10

Project Description:

Objectives: To describe in detail the sequential ultrastructural changes occurring as a response to a reproducible wound in the mouse brain.

Methods Employed: Same as in previous reports. In addition, special stains and light optical systems have been applied to the evaluation of the lesions.

Major Findings: This project has been divided into eight separate phases. Six of these phases have been completed and the seventh "Large Epoxy Tissue Section of Mouse Brain" was prolonged while the development of specific technical procedures was undertaken. Phase seven was completed and a demonstration showing the application of large epoxy sections to central nervous system investigations was prepared and shown as part of a general exhibit at three separate meetings.

Significance to Bio-medical Research and the Program of the Institute: This investigation has been undertaken to apply improved electron microscopic techniques in an effort to enhance and clarify existing knowledge pertaining to the response of the brain to trauma.

Proposed Course: Completion of the eighth stage of this project was again postponed. If time and facilities permit, it will be completed during the 1969-1970 year and afterwards the effects of diet, hyperoxygenation, anoxia, infection and immune response may be considered.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-66 PR/P 1354
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Automated Microspectrophotometry Employing the LINC Computer

During FY 1969 this project was incorporated with Serial No. NDS (CF)-65 PR/P 1278.

Serial No. NDS (CF)-66 PR/P 1355
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Factors Influencing Quantitative DNA Staining

Previous Serial Number: Same

Principal Investigator: Jack H. Carleton, M. D.

Other Investigators: Charles Spencer, M. D.
Lewis E. Lipkin, M. D.

Cooperating Units: Mortimer Mendelson, M. D.
Department of Radiology
University of Pennsylvania

Man Years

Total: .2
Professional: .2
Others: .0

Project Description:

Objectives: To devise ways of testing and to determine the degree of influence that various factors have on the microspectrophotometric measurements of DNA staining. Factors which are under investigation include stain fading, species and embryological development differences in absorption curve characteristics, and staining progressivity.

Methods Employed: Instrumentation and procedures used in this project have been developed under the direction of the investigators and include a specially constructed two wave length cytophotometer and a microscopic slide perfusion chamber. In addition, photographic methods have been employed to compare stain progressivity and evaluation of pictorial information has been conducted on a Zeiss Integrating Densitometer at the AFIP. Confirmation of this pictorial evaluation will be provided by direct microspectrophotometry (MSP).

Major Findings: The investigation of Gallocyanin and Feulgen progressivity in whole cells using the cell perfusion chamber developed in 1966 by photographic techniques has been completed and is awaiting correlation with MSP.

Significance to Bio-medical Research and the Program of the Institute: Greater understanding and documentation of the factors influencing quantitative DNA staining is mandatory if these methods are to become more useful tools in the microscopist's search to automate and quantitate the evaluation of the images. It is to this aim that this project is directed both for use within the Section's investigations of automated biological image processing and for this field of research in general.

Proposed Course: The evaluation of actual stain progressivity as measured directly on a microspectrophotometer has been postponed until the instrumentation becomes available.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/P 1649
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Congenital Malformations in Perinatal, Infant and Child Deaths

Previous Serial Number: Same

Principal Investigators: Luz A. Froehlich, M. D.
Toshio Fujikura, M. D.

Other Investigators: None

Cooperating Units: All Collaborating Institutions

Man Years

Total: 0
Professional: 0
Others: 0

Project Description:

To report the analysis of malformations on autopsied stillbirths, neonatal, infant and child deaths and to determine the underlying relationship of multiple and single malformations to sex, race, type of death, birthweight, gestational age and maternal age.

Congenital malformations in perinatal, infant and child deaths were analyzed according to strict criteria. Rates for each type of death and sex were consistently higher in whites than in Negroes. Single malformation rates in neonatal deaths were twice as high in males as in females. Multiple malformations were common in white females especially stillbirths. The general incidence was not significantly higher in the extremes of maternal age except in white females, where the high rate in those 19-years-old or less was mainly due to multiple defects. Malformations appeared to play a relatively small role in the premature compared to the mature baby that died. The lack of clustering of associated malformations at the specific critical time period when the selected malformation was expected to have occurred demonstrates the etiologic complexity of this problem in humans. This study has been completed.

Honors and Awards: None

Publications: Froehlich, L.A., and Fujikura, T.: Congenital malformations in perinatal, infant and child deaths. In Nishimura, H. (Ed.): Methods for Teratological Studies in Experimental Animals and Man--The Second International Workshop in Teratology, Kyoto, 1968. Tokyo, Japan, Igaku-Shoin, 1969.

Serial No. NDS (CF)-68 PR/P 1650
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Twin Placentation in Relation to Zygosity

Previous Serial Number: Same

Principal Investigators: Toshio Fujikura, M. D.
Luz A. Froehlich, M. D.

Other Investigators: Ntinos Myrianthopoulos, M. D.

Cooperating Units: All Collaborating Institutions

Man Years
Total: 0.5
Professional: 0.5
Others: 0

Project Description:

The relationship between type of twin placentation and zygosity was studied in 569 sets of twins. Monozygosity was higher in Negroes (24.9%) than in whites (18.2%). In separate Diamniotic-Dichorionic twin placenta, monozygosity was rare in both races (2.9% in whites and 5.6% in Negroes). Perinatal death rates, birth weight, gestational age, birth weight difference (ratios), gravidity, maternal age and major autopsy findings were evaluated in relation to twin placentation.

The paper is in preparation for publication.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/P 1651
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Ultrastructural Evaluation of Developing Hyaline Membranes in Strain A Mice

Previous Serial Number: Same

Principal Investigators: Toshio Fujikura, M. D.
Jack H. Carleton, M. D.

Other Investigators: John L. Priester

Cooperating Units: None

Man Years
Total: 0.3
Professional: 0.1
Others: 0.2

Project Description:

To determine the pathogenesis of hyaline membranes produced by oxygen poisoning.

Sequences of seven strain A mice (six weeks of age) were placed in a specially constructed positive pressure high oxygen cage and one animal removed every 24 hours. The animals were killed and the lungs removed, fixed and processed by the large epoxy section technique. Light and electron microscopic comparisons were then studied.

Comparisons of the light microscopy and ultrastructural changes occurring during oxygen poisoning are in progress; no conclusions can yet be drawn.

This study is temporarily discontinued.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/P 1652
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Ultrastructural and Histochemical Evaluation of the CNS in Mice Progeny when a Protein-Deficient Diet was Administered During the Second Half of Gestation

Previous Serial Number: Same

Principal Investigators: Jack H. Carleton, M. D.
John A. Churchill, M. D.

Other Investigators: John L. Priester

Cooperating Units: Dr. Carl T. Hansen
Genetics Unit Head
Rodent and Rabbit Production Section
Laboratory Aids Branch
Division of Research Services

Man Years

Total: .4
Professional: .2
Others: .2

Project Description:

Objectives: To elucidate any new anatomical changes induced in the brain by prenatal nutritional states and correlate these findings with reduced learning potential.

Methods Employed: One-hundred and eighty-one general purpose NIH mice (selected because of strain reliability to test situation) were time-mated prior to their first pregnancy. The beginning of fertilization was determined by the presence of a vaginal plug and no subsequent plugs. The females were divided into two categories which consisted of normal protein (26%) and no protein diets of equal calorie and supplement values. This diet was started on the tenth day of gestation and regular diet replaced when the mice were born. Some newborns were killed from each group, fixed in gluteraldehyde and embedded for large epoxy sections. At 21 days the mice were weaned. At one month of age, all mice will be tested under contract at Hazleton Lab by a one-way discriminating avoidance test. Selected animals were then perfused with gluteraldehyde or formalin and processed for electron microscopy or microspectrophotometry.

Major Findings: The comparison of ultrastructure, Feulgen DNA, and Gallocyanin Chrome Alum DNA-RNA has not been completed but will be evaluated and compared to testing results as instrumentation and technical time is available.

Significance to Bio-medical Research and the Program of the Institute: This investigation was derived to test the hypothesis and trend found in the PRB-Collaborative data that there is a relationship between proteins, intelligence and mental retardation. The project may produce the information necessary to permit a better evaluation of the absence or presence of submicroscopic lesions from intrauterine nutritional impoverishment.

Proposed Course: The material collected will be studied by the outlined methods and reported. Continuation of the project will depend on the outcome of this evaluation.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/P 1653
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Correlative Light and Electron Microscopic Pediatric Pathology

Previous Serial Number: Same

Principal Investigators: Jack H. Carleton, M. D.
Lewis E. Lipkin, M. D.
John L. Priester

Other Investigators: None

Cooperating Units: Division of Pediatric Pathology
Department of Pathology
Children's Hospital
Columbus, Ohio

Department of Pathology
Ohio State University
College of Medicine
Columbus, Ohio

Man Years

Total: .5
Professional: .2
Others: .3

Project Description:

Objectives: To apply the techniques of preparing large epoxy sections for light and subsequent electron microscopy (developed in our laboratory, Serial No. NDS (CF)-67 PR/P 1518) to a representative number of cases from pediatric hospitals and obstetrical departments. These specimens will be used to augment our own PRB pathology material by providing ultrastructural comparisons to conventional histopathology in the areas being investigated by the Project and, in addition, will serve as the basis for a possible unique atlas and teaching library of the ultrastructural aspects of pediatric pathology.

Methods Employed: Sixty-four autopsies were performed and 50 surgical specimens out of 1,400 surgicals were selected by the investigator for processing, using the re-embedding light and electron microscopy technique developed under Project Serial No. NDS (CF)-67 PR/P 1518. These specimens were fixed with gluteraldehyde and stored in buffer until embedding in plastic. Unstained H & E sections were cut for microscopic and ultrastructural evaluation and correlations.

Significance to Bio-medical Research and the Program of the Institute: Using our two-staged embedding procedures, an ultrastructural evaluation of pediatric diseases can be accomplished with a magnitude previously unobtainable at a greatly reduced investment of professional time. This submicroscopic investigation of newborn and neonatal pathology will greatly enhance our interpretation of the light microscope findings in our Project material and in the pediatric pathology community in general. It will also give us the ability to prepare a unique atlas and teaching library to compare pathology and normal conditions as seen by both light and electron microscopy.

Proposed Course: The material obtained is being processed to completion as technical time permits and will be for reference purposes.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/P 1763
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Kidney Malformations in Fetuses of ACI/N Strain Rats

Previous Serial Number: None

Principal Investigators: Toshio Fujikura, M. D.
Jack H. Carleton, M. D.

Other Investigators: None

Cooperating Units: None

Man Years
Total: 0.9
Professional: 0.5
Others: 0.4

Project Description:

Randomly selected pregnant rats, ACI/N Strain (A X C 9935, Irish) at the NIH colony were used for the study of spontaneous kidney malformations. The animals were killed at or near term for detailed examination of fetal and maternal malformations involving the genitourinary system.

Agenesis of one kidney occurred more often on the right side than on the left in both males and females. Renal agenesis was always associated with absence of a uterine horn on the corresponding side. However, the ovaries and the testis were present and intact. Cystic kidney was seen more frequently in males than in females. So far, pregnant rats with renal malformations were rare. The study is still continuing to determine the proper frequency of kidney malformations in the fetuses and their mothers. There was a close relationship between agenesis of kidney and cystic kidney.

A preliminary report will be presented at the International Teratology Society meeting to be held in Mount Ranier, Washington on July 7, 1969.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/P 1764
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Placental Study of Abortion Material (obtained by an induced abortion)

Previous Serial Number: None

Principal Investigators: Toshio Fujikura, M. D.
Luz A. Froehlich, M. D.

Other Investigators: Hideo Nishimura, M. D.

Cooperating Units: Department of Anatomy, Kyoto University
Kyoto, Japan

Man Years
Total: 0.05
Professional: 0.05
Other: 0

Project Description:

The present study aims to investigate the following points:

a. Normal histology of the early placenta (various histologic criteria of developing placenta)
b. Histopathologic findings of the placenta in spontaneous abortions as compared to induced abortions
c. The relationship between fetal malformations and placental or cord anomalies (such as single umbilical artery, abnormal insertion of cord, etc.)

According to Dr. Nishimura the materials are collected under close cooperation of 1,073 obstetricians. One distressing aspect of induced abortion materials is that over 90% of the fetal and placental specimens obtained are crushed or badly mangled and that perfect specimens become available only rarely. Therefore, gross examination of these materials is limited to intact specimens.

Dr. Nishimura will send me the placental slides with fetal and maternal information. The first shipment of the slides (approximately 103 cases) has been received and the placental collection of about 500 cases or more is expected to be finished in one year. This study is supported by the NICHD (HD-01401).

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/P 1765
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Interrelationship Between Selected Congenital Malformations and Major Pathologic Findings

Previous Serial Number: None

Principal Investigators: Luz A. Froehlich, M. D.
Toshio Fujikura, M. D.

Other Investigators: None

Cooperating Units: All Collaborating Institutions

Man Years
Total: 0.1
Professional: 0.1
Others: 0

Project Description:

The incidences of certain variables in the baby, mother and placenta of core death controls were compared with those deaths having selected congenital malformations. Velamentous and marginal cords were more common in single umbilical artery deaths compared to core deaths. There was surprisingly little association with diabetes, except among the cases with agenesis of the kidney. Meconium staining was nearly twice as high in multiple heart malformations compared to controls. Hydramnios was very common in association with anencephaly, and to a lesser extent with spina bifida and hypoplasia of lungs. The incidence of toxemia was more than twice as high in anencephaly, spina bifida, and agenesis of the kidney compared to controls. In addition, retroplacental hemorrhage was twice as high in anencephaly. Erythroblastosis was twice as high in accessory spleen but was not found in any of the other selected malformed cases.

The possible significance of these associations are now in the process of evaluation. The study is in progress.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/P 1766
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Reproductive Ability of the American Negro With Sickling and its Public Health Implications

Previous Serial Number: None

Principal Investigators: Toshio Fujikura, M. D.
Luz A. Froehlich, M. D.

Other Investigators: None

Cooperating Units: All Collaborating Institutions
Alan Chauvenet, DCRT
Ray Glass, Section on Pathology, PRB

Man Years

Total:	0.2
Professional:	0.2
Others:	0

Project Description:

The reproductive performance of 654 sicklers and 1890 non-sicklers in the Collaborative Study were compared. The cumulative fertility rate of mothers with sicklemia was the same as that of non-sickling mothers. There was no substantial difference in perinatal death rates, birth weight and gestation age between the sickling and non-sickling group. Only the infant and child death rate was higher in the sickling group. Because of the normal reproductive abilities of the sickler and despite various reported hazards of their disease, the sickle cell gene may continue to propagate in the U.S. Negroes for generations to come.

The paper is now being submitted to the Publications Review Board and the NIH Review Board.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)- 69 PR/P 1767
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Clinical Significance of Circummarginate and Circumvallate Placenta (Extrachorial Placenta)

Previous Serial Number: None

Principal Investigators: Toshio Fujikura, M. D.
Ralph C. Benson, M. D.
Luz A. Froehlich, M. D.

Other Investigators: None

Cooperating Units: All Collaborating Institutions

Man Years
Total: 0.1
Professional: 0.1
Others: 0

Project Description:

The clinical significance of completely circummarginate and completely circumvallate placentas was determined by an analysis of the records of 39,514 pregnant women and their offspring enrolled in the Collaborative Study. White women with circumvallate placentas had increased rates of antepartum bleeding, prematurity, neonatal and infant and child deaths, but not the stillbirth rate. Although similar findings were noted in the Negro circumvallate group, these were not considered unique for this group because these conditions were basically high in the total Negro population. The incidence of completely circummarginate placentas in white and Negro patients was 3.3 percent and 3.4 percent respectively; completely circumvallate placenta occurred in 3.6 percent and 2.0 percent of these women. Circummarginate placentas were not clinically important in either race. Extrachorial placentas were more common in multigravidas. Despite well established associated difficulties, extrachorial placenta is an uncommon, rarely critical clinical problem.

This paper in being prepared for publication.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/P 1768
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Bipartite Placenta

Previous Serial Number: None

Principal Investigators: Toshio Fujikura, M. D.
Luz A. Froehlich, M. D.

Other Investigators: Ralph C. Benson, M. D.
Shirley G. Driscoll, M. D.

Cooperating Units: Boston Lying-in Hospital

Man Years
Total: 0.1
Professional: 0.1
Others: 0

Project Description:

To study clinical significance on bipartite placenta.

Bipartite placenta represented 4.2% (366 of 8,505) of consecutive placentas of women enrolled in the Collaborative Project at the Boston Lying-in Hospital. Accessory or succenturiate lobe placentas were excluded. Bipartite placenta was associated with clinical problems such as antepartum bleeding and adherent placenta which required manual separation and/or extraction of the placenta. Despite these clinical problems, perinatal death rate was in the normal range. Older multigravidas (35 years) were more numerous in the bipartite group and a history of infertility was more frequent than in the total series. The etiology of bipartite placenta remains speculative although possible few factors are suggested.

The paper is in preparation for publication.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/P 1769
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: The Significance of Chorangiomas

Previous Serial Number: None

Principal Investigators: Luz A. Froehlich, M. D.
Toshio Fujikura, M. D.

Other Investigators: None

Cooperating Units: All Collaborating Institutions

Man Years
Total: 0.5
Professional: 0.4
Others: 0.1

Project Description:

To date 84 cases of chorangioma have been identified and verified by the investigators histologically, of which 5 were in twins and 4 terminated in stillbirths. By limiting the study to whites and Negroes only who have survived beyond one year, the number is reduced to 79.

A hand review of the OB-Ped records of these 79 cases suggests an increased association with hydramnios, toxemia, erythroblastosis, fetal hemangioma, single umbilical artery and minor bone and neurocutaneous abnormalities. There is a definite female preponderance and although there is undoubtedly some institutional difference in reporting, the condition seems unquestionably more frequent in whites. These differences have been mentioned in other studies, which also claim that prematurity is high in this group. However the prematurity rate in our surviving chorangioma group (8 of 79) was not different from that of single live births in the Collaborative Study (10%).

The incidences of selected variables in the chorangioma group will be compared with those of the control group, the latter consisting of all white and Negro survivors without chorangioma.

The frequency distribution tables of selected variables in the control population have just been received from the Section on Data Management and Retrieval. Analysis will proceed and material will be prepared for publication.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/P 1770
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Organ Weight/Brain Weight Ratios as a Parameter of Prenatal Growth

Previous Serial Number: None

Principal Investigators: Toshio Fujikura, M. D.
Luz A. Froehlich, M. D.

Other Investigators: Programming Staff, DCRT

Cooperating Units: All Collaborating Institutions

Man Years
Total 0.2
Professional: 0.2
Others: 0

Project Description:

A trial method was devised for predicting organ weights using given brain weight as the standard. This was based on the observation that brain weight unlike that of other organs is least affected by abnormalities of somatic growth. Except for the spleen, organ weight/brain weight ratios remained practically constant between 1,000 to 3,500 grams body weight. This suggests that the growth rate of visceral organs is proportionate with brain weight during the prenatal period. A small thymus was associated with visceromegaly in erythroblastosis. Small kidneys and lungs were observed in infants of toxemic mothers. The liver was small in Negro males and twins, two groups known to have high mortality rates. In twins, regardless of body size, a balanced growth was noted between brain and other organs. Brain weights in diabetes, toxemia, erythroblastosis and twinning were within the normal expected range.

A series of regression analysis programs adopted for our use by DCRT is being applied to refine the independent variable brain weight as a predictor of somatic organ weight. The effects of a series of transforms on brain weight data is in the process of being evaluated.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/P 1771
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Viral Infection in Pregnancy and Congenital CNS Malformations in Man

Previous Serial Number: None

Principal Investigators: T. S. Elizan, M. D.
L. A. Froehlich, M. D.
A. Ley, M. D.

Other Investigators: A. Fabiyi, Ph.D.
J. L. Sever, M. D.

Cooperating Units: Section on Pathology, PRB
Section on Infectious Diseases, PRB
All Collaborating Institutions

Man Years
Total 0.8
Professional: 0.8
Others: 0

Project Description:

The present study was undertaken to determine if there was a correlation between serologic evidence of maternal viral infection during pregnancy and the presence of a pathologically confirmed CNS malformation of the offspring.

Micro-complement fixation (CF) tests, using 16 viral antigens, and hemagglutination-inhibition (HI) test for rubella antibodies were performed on coded paired sera taken during pregnancy from 54 maternal cases with congenital CNS malformations in their offspring and from 104 matched controls with normal babies. Results of this study failed to demonstrate a correlation between serological evidence of maternal viral infection during pregnancy and fetal CNS anomalies. The observation that a considerable number of mothers with normal babies had serological evidence of viral infection during pregnancy should be taken into consideration when evaluating retrospective studies relating fetal malformations and maternal infection. This study does not negate the fact that certain viruses can and do produce congenital malformations. This study has been terminated.

Honors and Awards: None

Publication: Elizan, T.S., Froehlich, L.A., Fabiyi, A., Ley, A., and Sever, J.L.: Viral infection in pregnancy and congenital CNS malformations in man. Arch. Neurol. 20: 115-119, 1969

Serial No. NDS (CF)-69 PR/P 1772
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Pathologic Effects of Ligation of the Anterior Spinal Artery and/or the Great Radicular Artery in Monkeys

Previous Serial Number: None

Principal Investigator: Oscar Aparicio, M. D.

Other Investigators: Larry C. Fried, M. D.
Jack H. Carleton, M. D.

Cooperating Units: Surgical Neurology Branch
Intramural Research
National Institute of Neurological Diseases and Stroke

Section on Neuroradiology
Medical Neurology Branch
Intramural Research
National Institute of Neurological Diseases and Stroke

Man Years

Total: .15
Professional: .10
Others: .05

Project Description:

Objectives: The neuropathological evaluation of spinal cords of monkeys subjected to vascular ligations, in order to determine the practical feasibility of sacrificing any of these vessels if necessary during the course of a surgical procedure.

Methods Employed: The neuropathologic evaluation of the spinal cords by means of multiple staining methods, including H & E, Luxol Blue with Cresyl Violet, and others, in order to determine the presence, extent and location of any lesions due to ischemia.

Proposed Course: The specimens are being processed. The analysis of data is expected to be completed during the next few months.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-69 PR/P 1773
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Evaluation and Development of Neuropathology Special Staining Techniques

Previous Serial Number: None

Principal Investigators: Oscar Aparicio, M. D.
Jack H. Carleton, M. D.

Other Investigators: John L. Priester

Cooperating Units: None

Man Years

Total: .15
Professional: .10
Others: .05

Project Description:

Objectives: To evaluate and make modern practical application of a number of old special staining techniques which were very useful in the early development of neuroanatomy and neuropathology, and still have a great potential. To try to update some of these methods so they may be utilized in conjunction with other modern techniques in the evaluation of fresh specimens and also on tissues embedded in paraffin and in plastic for both light and electron microscopy.

Methods Employed: Experimental animals are being used. Many of them are previously subjected to manipulations to develop specific degenerative lesions in the central nervous system. The animals are then sacrificed and perfused with various fixatives. The brains are then processed and stained by the different methods under study.

Proposed Course: The study is only in the initial stages. Analysis of the material already processed is to be done. Further steps in the future will be determined by the results of this analysis.

Honors and Awards: None

Publications: None

Serial No. NDS (CF)-68 PR/SLH 1520
1. Perinatal Research Branch
2. Section on Speech, Language and Hearing
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1968 through June 30, 1969

Project Title: Explorative Study for the Use of a Speech and Language Screening Examination for 3-Year Old Children in the Home Situation.

Previous Serial Number: NDS-(CF)-63 PR/Bs 1167

Principal Investigator: Dr. Miriam F. Fiedler

Other Investigator: Dr. Eric H. Lenneberg

Cooperating Units: Children's Medical Center, Boston, Massachusetts
Section on Behavioral Sciences, PRB, NINDS
Section on Pediatric-Neurology, PRB, NINDS

Man Years:

Total:	.5
Professional:	.2
Other:	.3

Project Description:

The study concerns children with non-normal speech identified at age three years by means of interviews with the mothers of Perinatal Project children in Boston. Findings were confirmed by subsequent speech, language and hearing examinations. The speech data were considered in relation to perinatal findings as an initial study, and, in a second study, with regard to outcome at age seven years in the light of psychological and neurological examinations. Most of the children identified as abnormal or suspect at age three years were found to be similarly regarded by other measures at age seven years.

Part of the study was presented by Dr. Fiedler as a paper delivered at the Tri-City Meeting of the Obstetrical Society in Boston on May 16, 1967, under the title "Delayed Speech Development in Children at 3 Years of Age Related to Peri- and Postnatal Findings". The studies are in the final stages of preparation for publication, lacking only introductory material for completion.

Honors and Awards: None

Publications: None

HOW TO USE
THESE SEPARATORS

Use one page for each separation.

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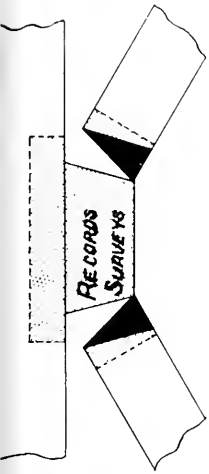

TABBED SEPARATOR SHEET
Form HEW-69
(3-56)

Annual Report
Associate Director's Report
July 1, 1968 through June 30, 1969
Extramural Programs
National Institute of Neurological Diseases and Stroke

The details of mission accomplishment of the Institute's Extramural Research and Training Program, as well as the specific problems associated therewith are included in the reports of the responsible Extramural Program Branch Chiefs. In broader administrative and scientific terms, however, the NINDS Extramural Programs for Fiscal Year 1969 have been characterized by:

A. An improvement in providing the required professional and administrative framework for the encouragement and support of research and training central to the mission of the Institute but yet responsive to the needs of the scientific community. A great deal of staff effort and time has been devoted to defining on an operating level the fine but critically important differentials between (1) mission-oriented directed research and the necessary non-directed, but mission-oriented growth of the neurological, visual, and communicative sciences and (2) providing for adequate stewardship of public funds yet avoiding administrative procedures which are burdensome to grantees and only of secondary importance to good management practices. The success of these efforts is dependent upon a continuing inter-action between the professional and administrative members of the staff and between the staff and representatives of the scientific community. This interchange has flourished during Fiscal Year 1969 and has been characterized by its constructive consequences. Reports from our advisory groups, consultants and grantees strongly support the Institute's philosophical approaches to program development and program management. A reorganization of the Research Grants Branch has helped provide a stronger base for this. In both the Research and Training Programs, the principles of organization focus upon the concepts of (1) each grant having a single manager responsible for both the professional and administrative aspects of the award, (2) each member of the staff being responsible for the development of broad disciplinary areas of research or training (e.g.: clinical neurology, basic neurosciences, human communications, etc.), and (3) specific members of the staff assigned to selected special areas of NINDS mission in accordance with scientific opportunity, program need, and staff skill (e.g.: L-DOPA, Stroke, Cerebral Death, Aphasia, Diabetic Retinopathy, etc.). This has provided a stable framework for the continuing, detailed operations of ongoing programs and the opportunity for special effort in selected areas of program responsibility.

B. A continuing increase in Extramural Program professional and administrative responsibility with an associated decrease in staff size and flexibility. The year has been characterized by additional increases in both the need for detailed professional decision making and grant negotiations and a steadily increasing number of managerial requirements originated by the Department of HEW and the NIH; concurrent with this assigned increase in responsibility and administrative procedure has been an eroding away of staff size and morale through personnel restrictions and minimally adequate personnel management practices; some examples of the latter include long delays in personnel

actions, lack of periodic reports on pending personnel requests, and the using of patterns of organization rather than the level of staff responsibility in the assessment of grade levels. The combination of decreasing staff morale and increasing responsibility poses serious threats to an operation whose administrative standards are those of excellence, and presents the danger of its conversion to one which will be satisfied with levels of performance that are minimal but adequate. Because of this alarming situation, Extramural Programs is faced with the need to develop methods by which the Institute can both discontinue specific Extramural Programs and decrease selected administrative operations of a non-legal variety.

C. A substantial deficit in required research and training funds, the latter being of such consequence that a complete reassessment and redesign of the Institute's Training Programs for Fiscal Year 1970 becomes essential. In both the Research and Training Grant Programs in Fiscal Year 1969, reductions in every grantees' budget were individually negotiated to a level at which further reduction in Fiscal Year 1970 would mitigate against the feasibility of attaining the grant's objectives. Because of this and a critical need to initiate selected new activities of high program relevance, a reassessment of Institute grant objectives and methods has been initiated. This is particularly true in the training area where factors need to be weighed such as the relative needs for additional academic and research personnel in the clinical sciences versus preclinical sciences; the relative importance of support of the training environment versus support of the trainee and the most appropriate administrative instruments of award in each area; the appropriate levels of trainee or fellowship stipend and the relative responsibilities of the training institution and NINDS in providing for these; and the point in a trainee's career when "career development" stability is most critical and productive. In addition, select committees of NINDS consultants are reviewing the national status of specialized clinical training, clinical personnel requirements for providing urgently needed patient care, and the role of the Federal establishment in providing for specialized clinical training.

D. Staff discussion and the preparation of an Institute position in regard to the over-all goals of the NINDS for the decade of the 1970's, particularly as these goals related to problems of clinical trials and to the development and evaluation of controlled community clinical demonstration and evaluation activities. In selected areas of national need, for example, trauma to the brain and spinal cord, the Extramural staff is exploring the feasibility of establishing carefully structured national centers of excellence for research, teaching and patient care as national models for community or regional action. In such national centers of excellence the differential among clinical research, teaching and patient care can be kept to an absolute minimum and a comprehensive program aimed at the total medical problem of the handling of the acute lesion of life threatening consequence and the prevention of permanent damage. It has been proposed that this "National Models Program" be launched on a pilot basis in selected problem areas such as trauma to the brain and spinal cord, epilepsy, and stroke; it would complement the NINDS active research project, clinical center and training programs in these same areas.

E. Selected areas of program responsibility have been given special attention, including (1) L-DOPA: Upon advice of an NIH panel of scientific experts, the Institute did not move forward with a prospective controlled evaluation of the efficacy and human toxicity of L-DOPA in the treatment of Parkinsonism. A retrospective analysis of available data indicated that L-DOPA probably was clinically efficacious, showed varying degrees of toxicity, and that the known adverse reactions were probably medically manageable. Two corporations in the pharmaceutical industry have launched clinical trials of the chemical in preparation for the submission of an N.D.A. to the Food and Drug Administration. The Institute is observing these trials, initiating selected studies of its own in areas not being adequately explored by the scientific community, developing 4-5 centers of research excellence for long-term studies of basal ganglia and extra pyramidal disease and its treatment through clinical center awards, and organizing workshops on specific scientific and medical aspects of biogenic amines and the nervous system; (2) stroke: having initiated 19 cerebrovascular clinical research centers through its clinical center and specialized research center programs, the Institute has now begun to select those centers in which long-term clinical research and laboratory efforts have the highest probability of success, and will discontinue the others. This "weeding out" process will take approximately two years at the conclusion of which up to ten clinical research centers will remain and serve as national focal points for research and training on problems of the cerebrovascular diseases; (3) human communication: a three-year effort has been completed in which the total national problem of human communication and its disorders has been assessed and a comprehensive report prepared describing the state of this national problem, the present efforts being taken to meet these needs, and plans for meeting them; appropriate parts of the report will be published and distributed. Using this report as a working document, the Institute will evaluate its own efforts in this program area and initiate selected additional activities as staff, funds, and opportunity permit; (4) visual disorders: retrolental fibroplasia, a previously major cause of blindness in the USA, has begun to reappear as a result of oxygen therapy of the acute respiratory distress snydromes of the premature. The Institute has initiated a cooperative study to develop methods by which blood oxygen tensions can be measured more precisely in clinical situations and more exacting standards of oxygen therapy established which will provide for metabolic needs but still be below dangerous levels of visual development. Also, because of the unsatisfactory status of therapy for diabetic retinopathy, the NINDS has inaugurated a cooperative study to evaluate the efficacy of presently available methods of therapy.

F. Staff reorganization and operational modernization. A formal reorganization of the professional and managerial staff of the Extramural Programs has been completed in order to provide for greater identification and authority where responsibility for program operation exists. As part of this, the Research Grants Branch has been sectionized and within each Section staff scientists designated in the areas of the basic neurological sciences, the clinical neurological sciences and the communicative sciences; the same designations occur in the training areas. Despite this reorganization, the principle of a single staff scientist having total responsibility for all professional and managerial decisions on any particular grant has been maintained. Also, the

operations of the data reports and analysis section, OAD, have been reorganized to provide for conversion of a marginal punch card data storage and retrieval system to one utilizing the computer facilities of both the DCRT and DRG. This will provide for greater efficiency of operation but at the cost of less flexibility in data management; these latter compromises are the result of restrictions on the recruitment of necessary technical and clerical staff.

G. The initiation of the activities of the National Eye Institute. A National Advisory Eye Council has been appointed, an orientation and planning meeting held in March 1969 and a regular meeting held in June 1969. In addition, with the assistance and cooperation of the DRG, the philosophical and operational dissection of the grant and award programs of the NINDB into the NINDS and NEI has been completed. During Fiscal Year 1969, the Extramural Program staff of the NINDS continued to carry all responsibilities for NEI grant and award programs. Because of the continuing attrition of personnel, however, the over-all percentage of NINDS staff time available for this has decreased and continues to grow less. In Fiscal Year 1970, the staff of NINDS plans to assist the newly designated staff of the NEI in a supportive role, instead of as the responsible agents of the new Institute. The techniques and guidelines for this have been developed and are now operational.

Annual Report
July 1, 1968 through June 30, 1969
Research Grants Branch
National Institute of Neurological Diseases and Stroke

Introduction

The name of the Institute has been changed twice during the past year. With the legal authorization for the establishment of a National Eye Institute on August 16, 1968 the name was changed to National Institute for Neurological Diseases. It was later changed to National Institute of Neurological Diseases and Stroke. However, these changes have not affected the mission or activities of the Research Grants Branch in that the research grant programs of the NEI have continued to be the responsibility of the Branch during FY 69.

The scientific approaches to, and the scientific advances made in the various disorder categories within the mission of NINDS are summarized in subsequent sections of this Report. Therefore, comments here are limited to a few generalizations pertaining to both scientific and administrative aspects.

About a year ago data became available from several investigators, most of whom were supported by NINDS, to indicate that L-Dopa (3, 4-dihydroxyphenylalanine) might be highly effective in the treatment of Parkinson's Disease. These preliminary data indicated that at least 50% of the patients showed remarkable improvement and another 25% showed appreciable improvement. Even though the doses were large and serious toxicity would occasionally develop, the therapeutic potential of L-Dopa was considered very important. A proposed cooperative study of 20 institutions to evaluate this therapy was disapproved by expert consultants with the hope that data already available might answer the major clinical questions of efficacy and toxicity. This turned out not to be the case. Further review of the situation indicated that studies already supported by commercial pharmaceutical firms to satisfy FDA requirements plus projects presently supported by NINDS and other agencies would soon provide needed clinical data without further support from NINDS. Perhaps the most important needs for the future are 1) the synthesis and testing of one or more analogues or potentials of L-Dopa which will be more effective with less toxicity and 2) the additional insight into the chemistry and metabolism of the brain.

Research supported by this Institute virtually eliminated retrolental fibroplasia by the discovery in the early 1950's that it was usually caused by the exposure of infants to high oxygen concentrations. The more recent use of oxygen for hyaline membrane disease and other respiratory distress syndromes in infants has reopened the whole problem. Investigators at five institutions have just begun a two year cooperative study to establish safe guidelines for oxygen therapy in the premature infant.

There is considerable concern about the increasing incidence of diabetic retinopathy and the lack of a really satisfactory treatment. The NANDS Council has recommended support for a Planning Committee on Diabetic Retinopathy to 1) review the literature 2) identify research needs in the natural history and therapy of the disease and 3) develop an experimental animal analogue. Support has also been provided for a series of three workshops over five years to explore the development of studies on specific aspects of diabetic retinopathy.

After several years of work, the NANDS ad hoc Subcommittee on Human Communications and Its Disorders has submitted a three-volume report with twenty-six specific recommendations. The report includes a detailed analysis of the present state of research and training in this area. The recommendations are presently under review by the Council. Their implementation would increase research and research training in Human Communications by about 100% during the next five years.

The NANDS ad hoc Subcommittee on Rehabilitation also has submitted an extensive report on problems of blindness rehabilitation; this report is under review by the newly established National Advisory Eye Council. The work is concerned with the concentrated application of systems analysis and conceptual models to the study of blindness and services to the blind in the United States.

A new administrative problem this year was the negotiated reduction of every research grant, competing or committed, in order to have funds to award a reasonable number of new and renewal grants. All grants were individually negotiated downward by an amount which would still allow the work to proceed, although productivity was unquestionably reduced.

The Research Grants Branch was fortunate in maintaining a stable and experienced staff during the year. The transfer to the National Eye Institute of work on vision and its disorders will result in the loss of one professional staff member and will lead to an increased work load for all other members of the staff, because the one staff member has been responsible also for several areas other than vision. Because of increased activity in the Special Programs, some research project responsibilities from that area will have to be reassigned. These changes will require that the staff member lost because of the transfer to the NEI be replaced as soon as possible.

This year 1,798 research grants were supported at a total cost of $67.8 million. Last year the comparable figures were 1,780 grants for $65.1 million. The numbers of grants and amounts of funds in the various disorder categories are shown in Appendix A.

COMMUNICATIVE DISORDERS

Progress in research in the communicative sciences supported by the National Institute of Neurological Diseases and Stroke has been highlighted by many valuable contributions to the general understanding of the underlying mechanisms and dynamics of normal human communication and the several diseases which impair it.

Sensory Processes

In the area of sensory processes one investigator reported three major accomplishments. Work progressed on 1) the determination of a general decay time constant in the peripheral and central auditory system 2) determination of the acoustic impedance at the human eardrum up to a sound frequency of 8000 Hz and 3) determination of subjective vibrotactile intensity as a function of vibration amplitude and frequency. Investigations of central auditory masking and comparison of their results with neurophysiological recordings have shown that single neurons as well as groups of neurons of the 8th nerve, the cochlear nucleus, and the superior olivary complex fire at a rate which is maximum near the onset of stimulation and decays exponentially with a time constant of about 50 milliseconds. The decay time constant, as derived from central masking and neural recordings, appears independent of stimulus and of the tonotopic location. The invariance of the time constant with the neural level and its direct reflection in a behavioral response strengthens the evidence for the linearity of the central auditory system.

Inner Ear

The ears of seven chinchillas with complete section of the tract were examined by electron microscopy, along with normal animals. Results show that the outer hair cells are supplied for the most part (although not completely), by the crossed efferents, whereas the homolateral efferents are restricted to the inner spiral and tunnel bundles. Input-output function for cochlear microphonics as well as whole nerve action potentials, were measured at 1000 Hz in the ears of three animals at 14, 17, and 96 days after tract section. Responses were also measured in three animals just before and after tract section. Some differences in response before and after tract section were present, but these were no greater than variations encountered among normal ears. An endolymphatic hydrops experiment involving a light microscopic study of guinea pig inner ears operated upon for blockage of the endolymphatic duct and sac has been completed. The essential findings were the presence of hydrops in all sixty-one operated animals and frequent demonstration of lesions in the sensory cells, spiral ganglia and stria vascularis at the apical turn of the cochlea; the vestibular neurosensory elements remained essentially unchanged. None of the control animals showed hydrops.

Hearing

Electrophysiological experiments on cats with several electrodes permanently implanted within the cochlea suggest that it is becoming reasonably certain that some types of deafness related to cochlear defects are at least within the realm of surgical therapy. Twenty-four chinchillas have been exposed to a series of moderate intensity noise. Results indicate that although group means were stable from week to week when the same noise exposure was used, individual values of temporary threshold shifts (TTS) varied greatly. The noise was increased to 124 dB SPL. A two-hour exposure at this intensity produced permanent threshold shift (PTS). Analysis revealed none of the tests of TTS, the presumed predicator of PTS, showed significant correlations with the final PTS. In another series of studies on loudness, one researcher reported that the Physical Correlate Theory applied to loudness judgements considers that twice subjective levels of self-generated (autophonic) sounds are equivalent to estimates of the increase in sound level required to project ones voice twice distance. The Physical Correlate Theory considers that subjective magnitude judgements of both distance senses, vision and hearing, are based upon experience with changes in distance. In utilizing a new technique involving intracellular recording on the isolated spinal cord of the frog, an investigator was able to determine whether in the central nervous system there occurred a natural spontaneous release of transmitter from the presynaptic terminals. There had been conflicting evidence concerning the origin of so called "synaptic noise". The investigator showed that after all elicited impulses were blocked by tetrodotoxin, miniature synaptic potentials could still be recorded at rates not significantly different from those before the administration of the drug. These results suggest that in the isolated spinal cord of the frog, the miniature synaptic potentials were analogous to miniature end-plate potentials at the neuromuscular junction.

Hearing Disorders

Work is proceeding in establishing norms for the various parameters of human stapedial and tensor tympani reflex actions in normal populations and to compare results in patients with various middle ear pathologies. The method employed uses both impedance audiometry and typano-manometry. Electrodermal audiometry has aided in resolving the controversial question concerning hearing impairment associated with Rh incompatibility. Results of this study strongly indicate lesions low in the central auditory nervous system (cochlear nuclei) or in the peripheral sensory-neural mechanism (cochlea), not at high levels in the central auditory system. This localization of damage is an important step in understanding the nature of the impairment and in facilitating more effective aid to the individual. Significant damage to the organ of Corti was found to occur when chloramphenicol was experimentally appled to the middle ear in a large number of guinea pigs. The study was conducted to histologically evaluate and localize damage resulting from the direct application of chloramphenicol to the window of the middle ear. Wide spectrum chloramphenicol has been widely used by otologists because of its effectiveness when applied topically

to the middle ear in cases of chronic refactory otitis media and following typanomastoid operations. The histologic results indicated that chloramphenicol used in this way produced hearing loss through extensive damage to the organ of Corti and variable damage to the stria vascularis in the basilar turn of the cochlea. These findings should alert otologists to the danger of using chloramphenicol topically in the middle ear.

Bone Banks

In one Temporal Bone Pathology Laboratory, a total of 67 pairs of human temporal bones were received within the first six months. In almost every instance the brain was collected simultaneously. These brains are prepared for histologic study in the Neuro-pathology Laboratory. The anatomical material collected from these various sources represent a broad variety of valuable pathology which in every instance involves cochlear and vestibular system or other structures of the temporal bone.

Comparative Hearing

Further work is continuing on the structure and function of the ears of lower vertebrates especially the lizard. The results will extend our understanding of the relations between the details of structure and performance of these ears as shown by cochlear potentials. These results will also provide a better estimation of the degree to which different lizard species have developed pitch discrimination in terms of place representation along the basilar membrane. In an investigation of the function of the round window in the frog, evidence has been obtained by blocking this window that it serves as a yielding point in the action of sound pressures on the inner ear, just as it does in the higher vertebrates. Substantial progress has been made in studies of the use of echolocation by bats in the location and identification of objects. This manner of object perception is being analyzed in an effort to determine the particular acoustic cues utilized by the bat in different situations. It has been found and verified that the bat used temporal information in the discrimination of distances.

Hearing and Heredity

In experimental studies in hereditary deafness, 125 patients in 35 families have thus far been examined in a hereditary deafness clinic. Three families with dominantly inherited low frequency hearing loss have been identified and special audiologic testing has permitted a clear delineation of this newly recognized genetic entity. In addition, several patients with unusual chromosome anomalies have been examined, resulting in a definite description of laryngeal abnormalities in the Cri-du-Chat syndrome. A new syndrome of cochlear deafness, high myopia, and intellectual impairment is presented. Four of seven siblings are affected in an inbred Amish family, indicating a simple autosomal recessive mode of inheritance. None of the mentally unaffected siblings are myopic or have hearing problems.

Speech

In otolaryngology and speech pathology one researcher pointed out that to understand and provide rational therapy for phonatory voice disorders, it is necessary to understand the behavior of the larynx during the production of both normal and abnormal vocal sound. Analysis of ultra high speed motion pictures of larynges supports the hypothesis that there are at least four types of normal laryngeal behavior employed in speaking: 1) open larynx, no vibration 2) closed larynx, no vibration 3) incomplete closure during phonation and 4) complete glottal closure during vibration. Analysis also reveals that the vocal cords are capable of independent vibration and are influenced by unilateral disease or other conditions. Differences in vibrational pattern between the two vocal cords causes rougher sounding voice when the composite vibration creates random irregular variations in the sound wave. In a study of aphasia, speech patterns were found to correlate with anatomical lesions. The study suggests the presence of two distinct types of aphasia occuring with sufficient frequency to warrant consideration as syndromes. Actually, it was shown that a large percentage of aphasics can be placed in one of the two groups on the basis of speech characteristics alone and that the causative lesions producing these distinctive groups arise from separate anatomic localizations. The anterior area appears capable of producing cliche type, over-learned speech patterns while the posterior area is necessary for the specific exact use of language. In 100 patients with aphasic syndrome, a lesion located anterior to the Fissure of Rolando (the speech area of the frontal lobe) was associated with low verbal output, dysprosody, dyscertheria, considerable effort and predominant use of substantive words; whereas posterior lesions (the speech areas of the parietal and temporal cortex) showed little effect on these features but resulted in paraphasia, press of speech, and lack of substantive words.

Antiviral Substances in The Cornea

Since the discovery [illegible] the first therapeutically active antiviral compound, IDU, its potency in treating experimental herpes simplex has been well documented by many researchers, and the effectiveness of the drug in man has been established in five double blind studies. The Food and Drug Administration has accepted it and it is now widely used clinically. The ability of corticosteroids to suppress herpetic stromal edema has been established and IDU can inhibit the deleterious effects of corticosteroids on epithelial disease.

The shortcomings of the drug have also become apparent. Its effective therapeutic concentration is limited by poor solubility, and the use of special non-aqueous solvents such as DMSO are of little help in increasing therapeutic efficacy. In addition to limited concentration, resistance (in tissue culture) develops rapidly. Although the drug can be given parenterally and has apparently saved the lives of several children with herpes simplex encephalitis, it is a poor drug for systemic administration. It is hydrolyzed rapidly and may alter the chromosomal patterns so that its use in only potentially fatal diseases seems justified.

In order to find better drugs, the correlation has been studied between tissue culture activity and in vivo activity against corneal disease. A precise double blind evaluation system for in vivo measurement of activity utilizing herpetic corneal ulcers has been developed. This allows one to relate the improvement in corneal disease due to treatment to the concentration of the compound in eye drops and to plot precise, reproducible dose-response curves. For the first time this allows a quantitative evaluation of the potency of topical anti-viral compounds (a type of ED50), the determination of meaningful therapeutic-toxic ratios, and the precise comparison of drugs in terms of attainable antiviral activity. The tools to permit a precise evaluation of antiviral drugs in vivo, and this system with IDU as the positive control, is now a standard system used by most drug companies studying antiviral drugs. It has also permitted an in vivo study of metabolic rate-limiting steps for antivirals, which is important because these compounds can act at multiple sites. Additive or synergistic antiviral effects can be quantitated as well as competitive and non-competitive reversal of antiviral activity.

With these methods a wide variety of newer anti-metabolites have been discovered. Some, such as cytosine arabinoside, were too toxic to be useful. Others, such as methylamino deoxyuridine. (MADU) lacked potency, but one, 5-trifluoromethyl-2-deoxyuridine (trifluorothymidine or F_3 TdR), was exceedingly potent, with almost no toxicity, and almost no propensity to stimulate resistance to the drug by the virus. In rabbits, it made herpetic ulcers heal rapidly and reliably and the drug was a superior antagonist of the tendency of steroids to make herpes worse.

Glaucoma

Currently the importance of aqueous humor dynamics is undergoing analysis. If the true facility is defined as the increase in outflow of the fluid from the eye with an increase in the intraocular pressure, then pseudofacility is defined as the decrease in the flow of liquid into the eye with an increase in the intraocular pressure. Pseudofacility is affected by the hydrostatic pressure and the colloidal osmotic pressure of the blood within the vessels of the eye, the intraocular pressure and the permeability of the vascular bed. The magnitude of pseudofacility could represent one of the regulatory factors in the maintenance of intraocular pressure. Secondly, total facility (true facility plus pseudofacility) is the value measured by tonography. Subtracting the value of pseudofacility from total facility, yields true facility (outflow via Schlemm's canal). The first determination of pseudofacility in the eye of man has recently been reported. Pseudofacility was 20% of the total facility or 0.06 ul/min/mmHg.

Visual Electrophysiology

Recent investigations indicate that the Electrically Evoked Response (EER), a technique for recording the occipital response to electrical stimulation of the globe of the eye, represents a new type of measurement promising potentially useful information on visual function. It is one of several types of stimuli other than visible light used by investigators to create the sensation of light.

Both EER and the Visually Evoked Response (VER) have been useful in studying the eye. Results of the present investigations show that the EER is a distinct and separate entity from VER, utilizing part of the same pathways as the VER but differing in several notable respects. There is measurably shorter latency of the EER than the VER of the same subjective brightness, which suggests that at least one step in the retinal transmission chain has been bypassed--the rod outer segment step, or possibly the whole receptor--with the bipolar or ganglion cells stimulated. Differences in amplitudes of EER and VER of the same subjective brightness were found. The non-selective electrical stimulus appears to activate in a nonspecific way many cell trains (collateral circuits) which do not contribute to the sensation of brightness. These noncontributory circuits seem to terminate their activity in the occipital region.

In EER, the investigators sum the responses to repeated stimuli on a small special computer which permits recordings from the scalp of the intact human being. The stimuli are induced through a low vacuum contact electrode (the active electrode) and a U-shaped silver foil electrode (the inactive electrode) applied to the periorbital skin. Although there is considerable variation of EER from individual to individual, the response for any one subject appears to be constant.

The investigators report that these preliminary investigations are being expanded to include more standardization studies and investigations of disease involving retinal disorders. Expansion of investigations into EER production by other scientists seems imminent.

Rehabilitation In Eye Disorders

The special problems of prescribing suitable aids for partially sighted children have been under investigation for several years. Findings show clearly that in children with a static level of visual impairment the lens needs re-evaluating at intervals to determine when an increase in power of the reading aid is required. The two principal reasons for the changing requirements are (a) decrease in ability to sustain accommodation for a close reading distance and (b) decrease in the size of the text the child wishes to read.

Retrolental Fibroplasia

Recently high oxygen therapy has been found necessary to save the lives of premature infants who develop respiratory distress. Approximately 40,000 infants need such treatment every year. Nearly 20 years ago work supported by this Institute showed that the excessive use of oxygen therapy in such infants was the principal cause of retrolental fibroplasia which almost invariably results in blindness. Subsequently it was shown that the disorder could be prevented in many cases by constant control of the oxygen concentration in the eyes of infants while under oxygen therapy.

Despite this information there seems to have been a marked increase in the incidence of retrolental fibroplasia since the use of oxygen therapy became justified in the past few years. Many hospitals do not have facilities to monitor arterial oxygen and the levels that are safe for the retina of the premature infant are still unknown. To attack this problem the Institute has just begun to support a cooperative study including investigators at five separate institutions with the objective of establishing safe guidelines for oxygen therapy to the premature infant. The study is designed to (1) develop an improved arterial oxygen tension monitoring device; (2) determine oxygen time-dose relationships to retinal changes; and (3) examine histologically any eyes that may become available at death after exposure to oxygen. It is expected that this study will make important progress in this difficult area in two years.

Neuromuscular Disorders

Myasthenia gravis and the various muscular dystrophies constitute the most prevalent neuromuscular diseases. The dystrophies encompass a large variety of clinical conditions and new dystrophic varients in both humans and animals are described each year. They are usually genetic in origin although dystrophic changes are observed in experimental animals subjected to nutritional deficiencies. On the other hand myasthenia gravis has been recognized as a clinical entity for several hundred years.

The symptoms of myasthenia gravis are related to impaired transmission through the myoneural junction although it has not been established whether the deficiency is prejunctional or postjunctional. In the latter case, it would signify a decreased sensitivity to the transmitter, acetylcholine. If the defect were prejunctional, it would suppose that acetylcholine synthesis or release in response to motor nerve stimulation is impaired. Current therapy is centered around the administration of anticholinesterase agents which decrease the rate of inactivation of acetylcholine at the postjunctional site. While this implies refractoriness of the postjunctional receptors, recent studies of miniature endplate potentials suggest that the sensitivity of the endplate to acetylcholine is unaffected in myasthenia. Identification of the primary cause of the disease may eventually be clarified by the use of guanidine, a drug which facilitates the release of acetylcholine from motor nerve terminals. If the defect resides in acetylcholine release, guanidine should be of dramatic benefit. If the defect is in acetylcholine formation, initial improvement should be followed by deterioration of transmission as stores are depleted. Results thus far indicate that guanidine may be of benefit to some patients while others are adversely affected. Tentatively, some investigators now conclude that the disease probably does not arise from impaired release of the neurohumor. However, the nature of the physiological defect may vary from one patient to another or with the severity of the disease.

Recent research has suggested that myasthenia gravis may be an autoimmune disease. Lymphoid hyperplasia of the thymus occurs in approximately two-thirds of all patients and occasionally thymectomy induces remission. The immunoglobulin fraction of the serum of some patients binds with the cross striations of skeletal muscle. Serum globulins from patients may also react with the nuclei of various cells, cytoplasm of the epithelial cells of the thymus, and ribonucleoprotein of skeletal muscle. The striations of skeletal muscle obtained by biopsy contained globulin in some patients, and globulin was found in the skeletal muscles of rats following intraarterial injection of the serum of myasthenic patients. According to this theory of the etiology of myasthenia gravis, the neuromuscular junction of patients is believed to be sensitive to a circulating neuromuscular blocking agent. However, efforts to directly test this idea by the administration of myasthenic serum into rats has led to conflicting results.

The muscular dystrophies have been variously associated with morphological, chemical or physiological changes in muscle, nerve, the circulation or the myoneural junction. A variety of animal dystrophies are available for experimental laboratory use. The various clinical entities observed in humans are classified mainly by histological and histochemical analysis of biopsy material. Much research in this area is concerned with the correlation of histology with electrophysiology of nerve and muscle, chemical analysis for the activities of various enzymes and alterations observed with the electron microscope.

Recently studies of the chemistry and structure of human actin and myosin have begun. Since these are the predominant proteins of muscle, detailed information of this nature may eventually prove of value in tracing the etiologies of various dystrophies via the pathways of protein synthesis.

A careful and detailed protocol for the evaluation of therapy in muscular dystrophy has been developed and is currently employed in two centers to assess the possible therapeutic effects of hexahydrocoenzyme Q_4 on the course of dystrophy of the Duchenne type. This material was found to be effective in the treatment of the genetic muscular dystrophy of the Bar Harbor strain 129 mouse. The substance is a derivative of coenzyme Q_{10}, reported useful in the treatment of Vitamin E deficiency myopathy in rabbits and hamsters.

Potentially important observation of the effects of a high oxygen environment on the early course of genetic muscular dystrophy in chickens has been reported. Exposure to a 70 percent oxygen environment allowed enzyme development in the microvasculature and breast muscle to procede at a higher rate in affected chicks for the first weeks after hatching. However, the effect was absent after eight weeks of continuous exposure to high oxygen. At all times a direct correlation was observed between enzyme activity of the blood vessels and morphology of the muscle fibers.

Neoplastic Disease

A variety of procedures are employed for the diagnosis of brain tumors reflecting the absence of a standardized, reliable methodology for this purpose. This results from the heterogeneity of brain tumors in terms of size, morphology, vascularity, and metabolic characteristics. The technique used is usually dependent on the training and experience of the clinician. Careful examination of the electroencephalogram taken together with the presenting neurological signs are often sufficient to both diagnose and localize certain tumors. Angiography, x-ray visualization of radiopaque substances injected into the major arteries traveling to the brain, is currently utilized extensively. Its efficacy is based on the rate and extent of filling of the cerebral vasculature and the appearance of abnormal blood vessels. The procedure is not without risk, since the materials injected are potentially neurotoxic if not quickly flushed out of the cranial vessels, or if used in high concentrations. Current research is oriented toward reducing the toxicity of these radiopaque materials by chemical modification of the molecule and by using diluents which retard movement of material out of the blood vessel into the parenchyma.

Tumors which selectively accumulate radioactive tracers may be localized by external scanning. In this instance, it must be assumed that the blood-brain barrier in the affected area has been modified to differentially allow influx of labeled molecules. However, a growing tumor often produced edematous tissue changes in the surrounding parenchyma, including modification of the blood-brain barrier. In these instances radiotracers may enter the brain and delineate the periphery of the malignancy. Human serum albumin iodinated with I^{131} or I^{125} which is maintained in the blood relatively long periods may be utilized for localization purposes under these two circumstances where blood-brain barrier modifications have been produced.

The metabolic characteristics of certain tumors may be utilized for diagnosis. Neuroblastomas synthesize catecholamines at a high rate and this is reflected in the urine by the presence of relatively large amounts of catecholamine metabolites. A potentially important method of diagnosis currently undergoing development is based on the observation that brain tumors synthesize cholesterol actively. When cholesterol synthesis is blocked by the administration of triparanol, a metabolic intermediate, desmosterol, appears in the cerebrospinal fluid. Using clinically standardized procedures for the administration of triparanol and the sampling of cerebrospinal fluid, the increment of desmosterol observed identified 80% of tumors and no "false positives" are found. It should be noted that this method may be used to follow the course of tumor regression following therapy and to check for regrowth or the presence of metastases.

Brain tumors are usually treated by surgery and/or radiation. Often these procedures are palliative in nature since vital brain centers necessary for life may be involved and cannot be extirpated or further damaged. However progress has been made in increasing the effectiveness of clinical techniques. Recent observations indicate that concomitant treatment with radiation and adrenocortical steroids increases comfort and prolongs life. Tumor regression has also been accomplished by surgical implantation of small radon pellets. Chemotherapy is not extensively used since agents effective in other organs generally cannot pass the blood-brain barrier. In certain instances the barrier is modified either within or around the neoplasm so that it may eventually be possible to administer effective compounds through the cerebral blood supply provided that systemic toxicity is minimized by dilution or isolation of the circulation. Cytotoxic agents placed directly in the cerebrospinal fluid have been effective in controlling meningeal leukemia, but solid tumors have not yielded to this approach as yet.

The incidence of tumors of the nervous system has recently been reported for the entire population of Israel for the years 1961 through 1965. The overall figure of 12.8 per 100,000 is similar to that observed in Sweden and the United States. However, for immigrants of European origin the incidence was 15.6 in contrast to 7.3 for immigrants from Africa. Gliomas accounted for approximately one-third of all histologically verified tumors and meningiomas for about one-fourth. The five year survival rates were 63% for the latter and only 21% for gliomas.

The cause of tumor formation is not known although evidence for a viral origin has been accumulating in the case of experimental animals. It is therefore of extreme interest that a cell free preparation of an experimental animal glioma has recently been shown to be capable of inducing tumor formation in hamsters. Furthermore, virus particles were identified in the precancerous tissue. It is obviously necessary to demonstrate unequivocally that the particles seen were actually viral in nature and that they were causally related to tumor development.

Multiple Sclerosis

A nationwide cooperative study beginning in April 1965 and involving ten University-based treatment centers has treated 197 hospitalized multiple sclerosis patients in acute exacerbation with ACTH and placebo by a double-blind technique under a strict protocol. Five methods of examination and evaluation were carried out before and at weekly intervals for a total of five weeks. Data on the multiple variables of each method were collected and analyzed by computer. A summary of the results shows that with appropriate randomization of patients and treatment, a therapeutic agent can be reliably evaluated in this disease. Careful analysis of data confirms the clinical impression that ACTH has a weak therapeutic effect, somewhat superior to placebo, detectable at the second and third weeks, but which is less definite at the fourth week following the beginning of treatment. Six to eight month follow up observations are not sufficient to provide significant information to determine the late effects.

Experimental Allergic Encephalomyelitis

The demyelinating effect of sera obtained from animals with experimental allergic encephalomyelitis (EAE) has previously been demonstrated in tissue culture. The use of this in vitro model system has been extended to a study of both lymphoid cells and serum samples from inoculated animals. Lymphoid cells were obtained from Lewis strain rats inoculated with either whole bovine white matter in complete Freund's adjuvant or with adjuvant alone. The lymphocytes thus obtained were included in the culture's nutrient medium. Simultaneously, the serum from the same animal was also included in the sister cultures; all cultures were then observed for possible demyelination. The following observations have been made: 1) both lymphoid cells and serum from an EAE inoculated animal produce demyelination in cultured cerebellum and spinal cord. Neither induced demyelination in cultured dorsal root ganglion from peripheral nerve 2) the reaction to cells and serum differ. The demyelinating reaction to serum is rapid, frequently beginning and completing its course within hours whereas the same pattern of change requires days to be completed after exposure to cells 3) preliminary experiments show that washed lymphoid cells maintained in an isolated culture, i.e., in the absence of nerve tissue, release demyelinating substances (antibodies) into their nutrient medium which then cannot produce demyelination in cultured nerve tissue.

Findings which help to explain why myelination takes place in some situations and fails in others and why synaptic connections are re-established on occasion have resulted from an extensive study of the development and myelination in culture of immature cerebellar tissue of the new born mouse. The evidence presented indicates an in vitro persistence of basic affinities between neuronal types. The results also suggest that juxtaposition may enhance myelinogenesis by increasing the number of potential contacts between Purkinje and other neurons.

The cerebellum from the new born mouse was used for study because it is extremely immature at birth and remains myelinated in vitro and in vivo for the first five to six post-natal days.

Cerebellar explants were placed either widely separated or in contiguous pairs. A striking difference in pattern of myelinogenesis and organization was apparent between single and contiguous explants. At 14 days only 14% of single explants were heavily myelinated as compared with 55% of those paired at random, and 86% of those in topographic continuity. It appears that the selective affinities between certain cells of the cerebellar cortex with which they might normally interact in vivo may influence and direct axonal regeneration leading to the re-establishment of synaptic relationships between contiguous explants.

A transient little known type of mononuclear white cell in the peripheral blood has been shown to synthesize a factor capable of breaking down myelin in experimental allergic encephalomyelitis (EAE). It has been postulated that this might also be involved in human demyelinating disorders such as multiple sclerosis. These sensitized cells (immunocytes) reproduced rapidly and demyelination was observed in cultures to begin within a few days after immunization, well before lesions appear in the central nervous system. This has broad implications in studying events preceeding demyelination in a wide range of autoimmune diseases. Utilizing cultures of these circulating immunocytes should allow intensive study of short term in vitro protein synthesis, circumventing the problem of binding action to target organs.

A rapidly increased percentage of monocytes undergoing DNA synthesis was revealed during the inductive phase of EAE by a morphologic study of peripheral blood smears. It was found that these cells usually occur in maxium numbers several days before the onset of CNS symptoms, and were virtually absent by the first clinical evidence of neurologic disease. Many of these cells were found to have an unusually high rate of metabolic activity, releasing substantial amounts of radio-active protein into the supernatent obtained by centrifuging the immunocytes. The presence of the immunocytes may be a signal of immune response of diagnostic value.

Amyotrophic Lateral Sclerosis

An endemic focus of amyotrophic lateral sclerosis (ALS) in the Kii Peninsula in Japan has been under investigation for some time. Included are epidemiologic, genetic, clinical, pathologic, histochemical and trace metal studies.

In the Mitogawa area of the Kii Peninsula a high frequency of motor-neuron disease has now been documented from fatality statistics and epidemiologic survey. Prevalence of ALS (a spinal muscular atrophy) is about one per thousand population, and of primary lateral sclerosis about two per thousand--both far in excess of that found in western countries or in other parts of Japan.

Mortality statistics reveal that ALS was responsible for 31 deaths out of 1,414 deaths in Kii area for the past 5 years. This is 10 times the average of the whole of Japan.

Though originally considered genetic, the Marianas form of ALS is now thought to be an exogenous disorder because of 1) discovery of the Parkinsonism dementia complex in these islands; 2) clinical and especially pathologic factors of both ALS and Parkinson's Disease in at least some instances of either entity 3) high frequency of ALS among non-Chammorros of Guam as well as on Saipan and Tinian, and possibly in New Guinea; and 4) the present study on the Kii Peninsula.

Four cases of ALS from Kii and three cases of ALS from other parts of Japan have been autopsied. Pathologic studies revealed the process of Alzheimer's neurofibrillary change and vacuolar degeneration in autopsied speciments of the ALS cases from the Kii Peninsula. These changes were previously thought to be unique to the Guam cases.

A collaborative study of lathyrism has been undertaken in India. This is pertinent because of the clinical consequences of chronic lathyrism (lateral sclerosis) and the possible implication of the cycad nut which can cause lathyrism in cases of ALS in the Marianas.

An excessive manganese content in the soil and water in Guam is the basis for emphasis on this metal and its possible effect in ALS. A manganese study in Guam suggested a possible concentration of cases of ALS and/or Parkinson's Disease among miners.

A recent study of environmental factors in the Mitogawa area has revealed a high content of manganese in soil and drinking water located in the area of mines which are currently not in use, and chemical analysis of rocks found in these mines showed a high concentration of manganese. Systematic chemical analysis of manganese in human nervous system tissues has been carried out by means of the neutron activation method. Normal distribution of trace metals including manganese in autopsied specimens of human brain have been found.

Parkinson's Disease

A most significant finding in the last two years has been the effectiveness of orally administered L-Dopa in the treatment of Parkinson's Disease. Of the first 100 treated patients reported on by one research center, 75% were improved from 20 to 100% in their disease symptoms. The greatest

effect was on rigidity and akinesia, though tremor was reduced as well. Improvement on most patients has extended up to 13 months and longer. It is clear that L-Dopa is unmistakably superior to any other drug heretofore available for the treatment of Parkinson's Disease. However, adverse reactions have appeared which restrict its clinical usefulness such as: nausea, vomiting, postural hypotension, cardiac dysrhythmias and involuntary movements. The relatively large doses necessary to achieve and maintain clinical improvement (up to 8 grams per day) has led to research for improved analogs or the combined use of L-Dopa with a decarboxylase inhibitor in an effort to more readily secure and maintain adequate levels of dopamine in blood and brain.

The therapeutic effectiveness of L-Dopa in Parkinson's Disease has raised the question of a disorder in catecholamine metabolism as an underlying cause. L-tyrosine, the immediate precursor of Dopa, does not improve the disease symptoms when administered. Studies in the turnover rate of labelled dopamine and norepinephrine do not indicate any disturbances in the metabolism of these amines, at least in extracerebral structures.

There are two predominant biochemical abnormalities in Parkinson's Disease. One is a decrease in dopamine, norepinephrine and serotonin in the basal ganglia and two, a decrease in neuromelanin in the substantia nigra.

A constant finding in both idiopathic and postencephalitic Parkinsonism is the degeneration of nerve cells in the nigra system and diminution of melanin in these nerve cells. The presence of neuromelanin appears to be essential for normal dopamine production in the substantia nigra and in Parkinsonism the melanin granules contain less melanin as compared to normal.

Chlorpromazine commonly produced Parkinsonism-like extrapyramidal symptoms and this may be related to the interaction of this drug with melanin in the substantia nigra or with an effect on catecholamine metabolism in the basal ganglia. Experiments have indicated that chlorpromazine stimulates melanization in certain cells, probably by activating tyrosinase which has been reported to be present in the substantia nigra. Theoretically, one might expect an activation of the substantia nigra tyrosinase to shunt tyrosine from the catecholamine pathway to the production of melanin. A reduction in dopamine in the nigra body would biochemically mimic changes in Parkinson's Disease.

It was the basic research on the biogenetic amines which led to the observation that dopamine was deficient in cells of the basal ganglia and hence to the trial first of dopamine and then of L-Dopa as a therapeutic agent. Various experiments have demonstrated that dopamine can produce marked increases in motor neuronal excitability and can enhance both flexor and extensor monosynaptic reflexes.

The chemical, dimethoxyphenylethylamine (DIMPEA) is of interest because it is considered to be a normal metabolite of dopamine and because of its possible relationship to Parkinson's Disease and mental illness.

Also in this regard is Mescaline 3, 4, 5-trimethoxyphenylethylamine. Both chemicals, when given by injection, produced a series of motor disturbances similar to those produced by cholinergic stimulation in the brain. DIMPEA was slightly less potent than Mescaline. Dopamine itself was found to be inactive in this regard; as was also homovanilic acid, the final metabolite of dopamine.

Convulsive Disorders

Epilepsy is a collective term applied to abnormal brain functions which are manifested in convulsive disorders. The spasms are characterized by sudden over-activity of the brain cells resulting in loss of consciousness, thought and self-control. The severity and longevity of the seizures depend upon the kind of epilepsy and the causes from which the disease has developed.

In epilepsy, known as "grand mal" the attack is most violent. The afflicted person may bite his tongue and invariably he loses control of his faculties. The recovery period is relatively long and requires a rest period after the attack is over. In "petit mal" the seizure is of a short duration, the attacks occur more frequently, sometimes as many as a dozen a day. Seizures are characterized by jerky movements of the muscles of the arms and neck. Included in this class are infantile spasms or quivering spells. If the area or areas of the brain can be located from which these abnormal electrical discharges emanate, the afflication is termed as "Focal" or Jacksonian" epilepsy. The seizure generally starts in the extremities and/or in one corner of the mouth. The affected part trembles violently. The trembling movement moves upwards. It either ends up in a minor seizure or the individual may lose consciousness just the same way as it happens in grand mal. By far the most common type of focal seizures is the one in which the discharging neurons exert their influence upon the metal processes as well as upon the muscles. The characteristic features of this type of "psychomotor epilepsy" are: sharp and sudden pain in the stomach, dreadful fear, flinging of arms aimlessly, smacking of lips, and other incoherent physical and mental behaviors. When a person regains his normal consciousness, the experience undergone during the attack is completely lost.

Epilepsy may be caused by several factors, such as brain damage, presence of a scar caused by a wound or an injury, drugs, congenital malformation, nutritional deficiencies, metabolic abnormalities, fever (in infants), infectious diseases (encephalitis, meningitis), brain tumors and abscesses. Heredity plays a very small role in the induction of epilepsy. If one twin develops epilepsy, the other one is likely to develop it also. However, parents with this disease do not necessarily have epileptogenic offspring.

The fundamental problem is to understand the basic mechanism involved in this disorder and to develop techniques to control it. A variety of techniques have been applied to the study of nerve cell activity. One important defect in epilepsy is the uncontrolled electrical discharge from nerve cells. A device know as the electroencephalogram (EEG) has been

developed which picks up electrical signals from the brain cells, amplifies them and records the impulses in the form of graphs. Electroencephalography is the most useful tool for both diagnosis and research. With its help electrical energy discharge patterns in groups of brain cells, and in various areas of the brain, are recorded. Also with the help of microelectrodes electrical activity of a single cell can be recorded.

Functionally, each neuron builds up a supply of electricity through the action of its metabolites. By repetitive activity of charge and discharge, the cells become overactive and fire off irregularly. The firing pattern may spread to other areas of the brain resulting in an epileptic seizure. When the neurons start firing again in harmony then the seizure is over. Brain waves so monitored give no indication of the individual's intelligence, thoughts, or his mental health. However, they provide strong clues as to whether or not a person has epilepsy. An EEG recorded during a seizure is likely to show unusually high bursts of energy release. The pattern indicates the type of seizure an individual has suffered.

Experimentally, epilepsy has been induced in animals with the use of various chemicals such as antibiotics (penicillin) and by the injection of metals and/or metallic oxides. Investigations with iron hydroxide, magnesium hydroxide, zinc oxide, chromium oxide, and mixed earth oxides showed that all these oxides or hydroxides are without epileptogenic effect when applied to the motor cortex of the monkey. On the other hand nickel and antimony proved most epileptogenic only when implanted as pellets into the motor cortex. Mild effects were observed with bismuth, zirconium, tin, titanium, molybdenum and tungsten. Twenty three more metallic powders have been tested on the sensori-motor cortex of monkeys. Some have shown very severe effects, while others remained ineffective.

Monkeys with temporal epileptogenic foci began to show seizures without loss of consciousness two months after the alumina cream was injected. Monkeys with an occipital focus had no clinical seizures, but developed EEG spikes in the ipsilateral occipital cortex a month after the alumina injection. The aim of these studies is to elucidate the neural mechanism involved in the transition of a localized lesion in the brain to an epileptogenic zone. This type of experimental approach has contributed new methods of inducing chronic epilepsy in animals which provides an important new tool for the study of this disease. Applying EEG techniques to these experimentally induced epileptic animals, efficacy of new drugs is being tested, epileptic loci (foci) have been determined, and new and improved surgical techniques for therapeutic application are being developed.

Treatment of epilepsy is concerned primarily with the medical and surgical approaches. Before surgery is performed, it is necessary to ascertain that the seizures originate wholly or in part from an area of the temporal lobes that can be safely removed without causing serious neurological damage; the seizures occur frequently and are incapacitating and presently available drugs are ineffective in controlling the seizures. Also, the surgery must be accomplished so as to avoid creating a secondary scar which

may in turn cause recurrence of the seizures.

Several physio-chemical differences between normal and epileptogenic tissues have been observed. Notable of these is that the tissue from the areas giving rise to abnormal electric discharge did not bind to itself nearly as much acetylcholine as did the normal tissue. This metabolite has been shown to occur in high quantities in epileptic regions of the brain, which suggests that when this substance accumulates, seizures result.

Nerve excitability is greatly influenced by variations in the chemical constituents of the fluids both inside and between the cells. Factors that modify the balance of these constituents, such as sodium and potassium, require a great deal more investigation. A series of amino acids, such as gamma aminobutyric acid (GABA), have been shown to be involved in the excitability of nerves. In this connection, a deficiency of vitamin B6 (pyridoxine) has induced seizures by producing a deficiency of GABA. Also a number of know convulsant toxins appear to interfere with the use of GABA in the body. Disturbances of electrolyte balance may be related to the common convulsion during fever in infancy. Information about the cause and correction of such disturbances may be applied to reduce the severity of recurrent epileptic attacks and to reduce the possibility of permanent brain injury which may be caused by such episodes.

Hypothermia (90° - 92° F) as a tool in therapy of patients with acute cerebral lesions such as: cerebral contusions, cranial hemorrhage, tumors and cardiac arrest has been tried. Patients that were in status epilepticus, or had intermittent seizures which could not be controlled by medication, were completely relieved of attacks or at least were benefited by cooling. Local cooling of the epileptic brain resulted in the suppression of spiking activity which also facilitated its response to anticonvulsant drugs. From this study it was concluded that hypothermia is another treatment for problems of status epilepticus where drugs are not effective or are contra-indicated. In this treatment no complications were observed that could be attributed to the hypothermia.

The treatment of epilepsy has depended to a major extent on drugs. One of the earliest medications, was a sedative called bromide. This was followed by another sedative, phenobarbital, which worked better but caused drowsiness in some cases. About twenty years ago diphenylhydantoin (Dilantin) was introduced in the treatment of epilepsy. It has been widely used and has proved to be a valuable anticonvulsant drug. However, it was soon recognized that ataxia sometimes occured as a complication of therapy with this drug. The ataxia may develop rapidly over a period of a few days or insidiously over weeks or even months. One unexplained feature about this ataxia is the fact that occasionally a patient will rapidly develop ataxia in spite of having taken the same dose of Dilantin for several years. It has been held that ataxia is a benign symptom only requiring a reduction in dosage or occasionally withdrawing of the drug. It was, however, later conclusively shown that cats subjected to Dilantin medication had developed severe loss of Purkinje cells in the cerebellum and cystic gliosis of the cerebellar white matter. A number of cases of permanent damage to the cerebellum, apparently

due to this drug, have also been reported.

Further investigation on the epileptic patients, who had suffered Dilantin intoxication indicated a high level of CSF protein levels during the period of intoxication. All the patients improved when the drug was withdrawn, but abnormal signs occasionally persisted for several months. Inhibition of the Na, K, Mg, ATPase enzyme system by Dilantin was observed which may be an important factor in causing neuronal damage. It is suggested that Dilantin intoxification may not be such a benign complication as was previously thought, but this still does not alter the fact that Dilantin is probably the most effective single drug presently available in the management of epilepsy.

The need of potent drugs of low toxicity is still paramount, especially in psychomotor epilepsy. The use of Dilantin, phenobarbital, primidone, and mephenytoin (Mesantoin) has left a relatively large group of inadequately responding patients. Recently considerable interest has been centered on the use of benzodiazepines in the treatment of epilepsy. Diazepam (Valium) has been proved to be effective in the interruption of epileptic seizures. Similarly, chlordiazepoxide (Librium) and especially nitrozepam (Mogadon) have been shown to be useful in prophylactic treatment.

Oxapepam (Serax) which is a metabolite of diazepam is easily absorbed from the intestines and is excreted quantitatively, or nearly so, as the glucuronide. Oxazepam has been widely used as an ataraxic because of the large safety ratio and the infrequent occurrence of side effects (drowsiness, ataxia, skin rash, headache, etc.). Clinical trial made it clear that Serax is a potent drug in the treatment of psychomotor epilepsy and is of low toxicity compared to Dilantin and other anticonvulsant agents. The effect is seen not only in the reduction of seizure frequency but also in the EEGs. The fact that this compound does not interact with Dilantin metabolism, facilitates its use in combination with Dilantin.

Investigations on convulsive disorders are supported by fifty-eight research grants amounting to $2,790,000.

Infectious Diseases

Infectious diseases of the nervous system include many types of illness and an equal number of research tools are employed to attack the problems. Epidemiological studies in man or animals frequently indicate whether a disease is infectious, how it is transmitted and perhaps some idea about the causative agent.

Methods most commonly employed for recognizing the presence of viral agents in cell cultures include: observations for cytopathic effects, hemagglutination, hemadsorption; interference, fluorescence and electron microscopies. With electron microscopy and immunological techniques, efforts are made to detect infectious agents. Immunofluorescent techniques are being used in diagnosing and studying brain inflammation due to viruses. Other studies are concerned with experimental encephalitis; the epidemiology of

Eastern equine encephalitis; the effects of parasites on the nervous system; testing vaccines for protection against arboviruses; and the possible role of viruses in acute neurological syndromes in children.

Other work that is being investigated includes: the after effects of infections during pregnancy where they may result in brain damage and mental retardation; analysis of viral polioencephalomyelitis in animals; an experimental measles encephalomyelitis; the mode and spread of a variety of neurotropic agents; and increasing research on the so called "slow virus" diseases which there is reason to believe may be especially important in a variety of diseases of the nervous system.

Several years ago a viral polioencephalomyelitis was identified in pigs. The virus has now been isolated from several different organs and has been shown to be an enterovirus quite unrelated to many other known viruses. All isolates but one produced polioencephalomyelitis in germ free pigs indistinguishable from naturally occurring infections.

Recently an agent causing paralysis of the CNS in rats has been isolated and is called hemorrhagic encephalitis of rats (HER). It produces acutely lethal encephalomyelitis when injected into suckling rats, including severe hemorrhagic lesions of the brain and spinal cord.

Transmission of encephalomyelitis from humans to animals and further from animal to animal, producing symptoms typical of subacute sclerosing panencephalitis (SSPE) syndrome in the animal, has provided an important new lead in isolating and understanding the causative agent in SSPE. This disease of children and young adults is characterized clinically by progressive intellectual deterioration, myoclonic jerks, and coma. The patients become severely emaciated and die from intercurrent infections. The diagnosis established during the incipient stages often shows a personality disorder or mental retardation. At that time the EEG shows slowing and dysrhythmia. However, high amplitude, low frequency synchronous waves do not develop until the patient exhibits myoclonic jerking. Spinal fluid proteins and cell counts remain normal or increase slightly during the entire course of the disease.

It has been suggested that SSPE is caused by an infection with measles virus. Indirect support has been derived from the close match between the curves representing the presence of measles antibodies in a non-selected population as a function of age, and the cumulative plot of the age of onset of SSPE. Since immunofluorescent studies seem to have ruled out the possibility of distemper virus, little doubt is left that SSPE is associated with the measles virus and the possibility that other etiological agents must be considered has become remote though not entirely disproven.

The most obvious question is concerned with the discrepancy between the clinical and pathomorphological expression of measles encephalitis and SSPE. The former is primarily an acute condition, sometimes fatal within twenty-four hours, which develops within a few days after, but sometimes prior to the exanthema. The latter runs an exceedingly chronic, remittent course with an insidious onset after the exanthema from four to seventeen

years with an apparent incubation period of eighteen months. Admittedly, this kind of measles encephalitis has not been proved to be due to a virus infection of the brain tissue. In fact, demyelination patterns together with the post-exanthematous onset have provided powerful arguments in support of an allergic encephalitic syndrome.

On the other hand, the so called incubation type of measles encephalitis manifested before the outbreak of the exanthema has always been interpreted as indicating a direct viral aggression against the brain. This view is supported by the experimental induction of clinical measles in animals five days after subcutaneous and intranasal inoculation with brain emulsion from a patient who died with acute measles encephalitis.

This comparative account illustrates that the difference between measles encephalitis and SSPE may be more apparent than real. One report indicates an instance of measles encephalitis which showed the classical features of SSPE years later.

A somewhat different aspect of the problem is provided by the concept of slow infections and slow viruses. Slow viruses are capable of producing an eminently chronic progressive disease following an incubation period of several years. This concept has been fruitful in respect to Visna, Scrapie, and Kuru. The inclusion of SSPE in this group finds support on clinical and patho-anatomical grounds. Just why the measles virus produced an acute encephalitis syndrome in some cases and behaves as a slow virus in another needs further intensive investigation.

Myxoviruses are medium sized, ether sensitive RNA viruses, which in man have the common effect of causing respiratory disease. Although they are not regarded as "neurotropic" viruses in man, mumps is the most common virus causing central nervous system infection in rodents. In these studies occasional neurons are infected by the unadapted strain and repeated passage has yielded a strain which infects parenchymal cells of the brain causing acute encephalitis. However, mumps virus in hamsters has been shown to cause a clinically inapparent infection limited largely to ependymal cells and neurons resulting in acute encephalitis.

Hydrocephalus may be caused by infectious agents contracted prior to birth. Suckling hamsters infected by mumps virus, developed a narrowing of the aqueduct of Sylvius and subsequently hydrocephalus. The narrowing of this canal responsible for draining the ventricles of the brain is the most common cause of hydrocephalus in man.

The study was conducted with experimental models to determine the histopathological changes in the brain during acute infection, and the aqueductal narrowing and hydrocephalus induction. The signs of clinical disease developed only after the resolution of the acute infection (about fourteen days) during which the lining cells of the aqueduct had been almost destroyed. Of the suckling hamsters inoculated with mumps virus, ninety-five percent developed clinical hydrocephalus. These and other histological changes were shown to be specifically related to the mumps virus infection.

Infection of human lymphocytes with herpes simplex virus apparently does not vary with the age of the host as it does in mouse macrophages. There was no obvious difference between the number of infected adult and neonatal cells. The addition of phytohemagglutinin greatly increased the number of infected cells in both types. Intramuscular inoculation of herpes simplex virus in rabbits failed to produce CNS disease. Intrasciatic inoculation caused hind leg paralysis with an ascending myelitis. However, unlike the neural spread in mice, no evidence of viral growth could be demonstrated in the nerve. This suggests a different mechanism of neural spread in different species. In a pilot study, rabbits immunized with herpes simplex virus survived a large dose of HFEM virus. Injection of adrenalin appeared to reactivate the virus with clinical signs of encephalitis in one month. A study of fixed rabies virus in mice showed that the infection was limited mostly to neurons of the rhinencephalic structures, brain stem nuclei, dorsal root ganglia, anterior horn cells, and cerebellar Purkinje cells. After subcutaneous inoculation of the virus, it spread rapidly to the CNS via peripheral nerves without evidence of infection of the endoneural cells or any extraneural tissues. Work with the Sindbis encephalitis virus in mice demonstrated a precipitous development of resistance during the second week of like, due apparently to a limitation in the spread of infection. No nonspecific viral inhibitors could be detected. Studies on mumps virus encephalitis in hamsters showed that disease and death resulted from the infection of neurons which remained morphologically normal. It is suggested that this material may be useful in investigating the "slow" viruses which seem to act in a similar way.

In Schilder's encephaloclastic sclerosis, virus-like particles were identified by electron microscopy which are distinctly different from those observed in the case with herpes simplex encephalomyelitis, but are similar to those that occur in subacute sclerosing leukoencephalitis. The nature of these virus-like particles is being investigated.

Investigations on infectious diseases of the nervous system are supported by thirteen research grants amounting to $550,000.

Cerebrovascular Disorders

In 1969 cerebrovascular research support approximated $5,407,000. This represented 95 grants, 19 of which are clinical research center grants, the remaining 76 research grants. The latter includes cooperative studies. Although individual researchers continue to pursue investigations in specific aspects of cerebrovascular disease, the main thrust of the Institute's program is in the clinical research centers, wherein teams of investigators representing basic scientists and clinical investigators coordinate and interrelate their efforts in laboratory and patient-oriented research. The number of clinical research centers has not increased in 1969 over 1968 but this should not necessarily be construed as a lack of interest. The rapid growth which made possible the establishment of 19 centers within 3-5 years more likely predicates that we may now be supporting the major clinical and basic research teams which can constitute a research center. The difficulty of attracting new young investigators to such centers remains a serious

problem as is the difficulty of establishing new research centers in institutions which have a small core or perhaps even only 1-2 investigators interested in cerebrovascular research.

Highlights of progress as reported from several of the research centers will be reported as examples of the ongoing activities in the centers. One center now in its third year of operation is making clinical and laboratory evaluations by a multidisciplinary group, which are focused through a specially designed environment-controlled dynamic angiography laboratory in an attempt to define the alterations of aortocranial hemodynamics that result during limb exercise and changes of head/body postural relationships; and the manner in which hemodynamics may be altered by other pathophysiologic and mechanical factors. They place special emphasis on the correlation of clinical information with the results of "radioisotope arteriography", cerebral perfusion estimates by inhalation and arterial injection of ^{133} Zenon, analysis of pulsations detected by ultrasound, catheter contrast aortography and angiography, and direct measurements of blood flow in extracranial arteries by electromagnetic flowmeters during reconstructive surgery. They hope by their studies to provide a base for development and evaluation of diagnostic tests, analyze and evaluate the results of treatment, and establish correlations of predictive values which may aid in the identification of stroke-prone individuals in large population groups. In their studies on the development of ultrasonic techniques for the investigation of cerebrovascular disorders, routine midline echoencephalography in three positions, which includes evaluation of pulsations and of ventricular size, is performed on all patients in the study. They are able to record simultaneously the pulsations from three separate areas of brain to relate the arrival delay at each point in reference to the R-peak of the ECG. Preliminary results indicate a direct temporal correlation between pulsation arrival and significant extracranial arterial stenosis. These studies will continue.

Another study being carried out at this center is on radioisotope arteriography to obtain estimates of regional blood flow. The potential of the system, a gamma (Anger) camera, multiparameter pulse height analyzer, and computer compatible magnetic tape, is being evaluated and on the basis of 1500 studies, it seems to be a highly effective tool with particular promise in the area of mass screening of patients with asymptomatic carotid bruits. Valuable information can be obtained concerning silent carotid artery stenosis and occlusion, occlusion of major leptomeningeal arteries and arteriovenous malformations, and when combined with rectilinear brain scans is a valuable adjunct in the differential diagnosis of positive brain scans due to tumor and infarction.

Another center reports the completion this year of a 4 bed intensive care unit and a monitoring systemfor ECG, EEG, respiration, blood pressure and temperature. It also includes alarms and the opportunity for automatically started continuous tape recording of cataclysmic events portended by changes in these parameters. A master control panel is provided at the nursing station, and O_2, CO_2 and suction are available at each bedside. Study of patients in the ICU are just beginning as a result of the availability of the ICU. On the other hand, it should be noted that difficulties are already apparent inasmuch as the availability of highly skilled specialty

nursing staff "around the clock" for research patients in the study poses logistical problems, the solutions to which are presently being sought. A clinical study is being developed to evaluate urokinase therapy in selected stroke patients. A protocol is being developed as are plans to obtain the necessary urokinase. Reports of progress will be made at a later date.

In this center as in others, the Anger camera is also being used to attempt a more detailed evaluation of cerebral blood flow. An interface is being built between the Anger camera and a PC computer which is currently being programmed to plot changing brain isotope content observed following the intra-arterial injection of inert gas to calculate and contour-plot regional cerebral flood flow in ml per 100 gms per minute. This group has been able to obtain a matrix of regional brain blood volume following intravenous administration of radioactive nondiffusible indicator. They plan to normalize the data and then assess regional alterations following photic stimulation.

Another study by this center relates to the work with radioactive oxygen-15. This is carried out by having the patient inhale air tagged with oxygen-15 once, and then following the rate of formation of water by brain tissue and the rate of equilibration of the tagged water thus formed with the body pool. Earlier, inhalation experiments were done almost exclusively but intra-arterial injections of blood tagged with oxygen-15 oxyhemoglobin gives a very similar picture in terms of the formation of water and the equilibration of water with body water. In patients with either vascular occlusive disease or with brain damage there has been a difference between the two hemispheres in almost all of the cases examined so far. During the past 6 months, this group has concentrated on building a special 6-probe collimated helmet that will allow the simultaneous measurement of identical points over 3 areas in each hemisphere. This has been used several times and the group reports excellent results. They hope that a more regional assessment of oxygen utilization can be made by this technique. The use of oxygen-15 presents some difficulties because of its high gamma value (511 Kev.).

Earlier annual reports refer to the variety and complexity of research problems to which the cerebrovascular clinical research centers address themselves. These problems by no means diminish in variety or complexity. Indeed, as investigations continue it becomes apparent that the complexities increase. Problems particularly relating to terminology, acceptance of specific definition of terms are of especial importance in insuring the relevance of results from one group in the hands of another group. For this and other important reasons, the annual workshops for program directors and selected staff of the research teams in the CV research centers becomes invaluable. The third workshop was held in January 1969. The indepth review was devoted to diabetes and the concurrent discussion groups were directed toward 1) Lipid Metabolism 2) Cerebral Arterial Spasm 3) Mechanisms in the Control of Cerebral Circulation and 4) Computer Retrieval of Neurologic Data.

It is now well-established that patients with severe hypertension are less likely to have strokes if their blood pressure is treated. There is little consensus when blood pressure is only moderately elevated or when it is intermittently elevated. Some evidence suggests that acute hypertension may actually induce cerebral arteriolar constriction and increase cerebral vascular resistance, or cause rupture of microaneurysms leading to a cerebrovascular syndrome. On the other hand, there exists opposition to antihypertensive therapy on the basis that the reduction of blood pressure in the face of arteriosclerotic cerebrovascular disease may induce cerebral thrombosis. The problem of whether treatment of mild cases of hypertension will prevent strokes or increase their frequency, especially in the elderly and arteriosclerotic, has never been established. There are two primary questions to be answered 1) Does drug treatment in moderate hypertension reduce the cerebrovascular recurrence rate? 2) Does blood pressure reduction influence prognosis? These are not necessarily the same questions unless one has the most accurate information possible concerning cooperation in taking medication and concerning the change in blood pressure induced.

The magnitude of the problem is substantial and requires the collective effort of neurologists and internists to arrive at some solution. The best way to solve this important therapeutic dilemma is by a cooperative (multi-institutional) clinical trial. For the past three and a half years, the National Institute of Neurological Diseases and Stroke has provided grant support for study of the long-term effect of a fixed antihypertensive therapeutic (thiazide plus rauwolfia) program on the recurrence rate of strokes in ambulatory patients with mild hypertension. Several types of strokes are included in the study, among them transient ischemic attacks and single completed episodes. Unbiased information concerning the possible deleterious effects of blood pressure lowering is being collected also, so that the precise advantages or limitations of antihypertensive therapy may be discovered. Eleven university clinics located in various parts of the United States are participating in this cooperative study. The treatment regime is consistent with that currently used in general practice and therefore generally applicable.

Preliminary studies indicate that 1) the incidence of cerebral thrombosis as well as cerebral hemorrhage can be reduced by effective long-term antihypertensive treatment; 2) cerebral atherosclerosis is not a universal prerequisite for an ischemic cerebrovascular episode; other factors favorably influenced by lowering the blood pressure may also play a role; and 3) the effects of antihypertensive therapy on stroke recurrence in cases of less severe hypertension require further study; therefore registration of new patients continues. It is anticipated that follow-up with replacement of losses will provide sufficient numbers of patients over a five-year period to answer the question posed, "Does the reduction of blood pressure affect the recurrence rate of stroke?" The investigators participating in the cooperative study believe that clear-cut answers may in some part become apparent.

At the present time antihypertensive therapy is used regularly without conviction. At the least, this cooperative study should provide data concerning the benefit or risk of prolonged lowering blood pressure in persons with cerebrovascular disease, at all levels of age and vascular deterioration.

Trauma (Head Injury)

In 1969, 50 research grants investigating specific problems in head injury were supported representing $1,900,000. Seven grants to develop head injury centers are now attacking problems in head injury in a multidisciplinary or multifaceted approach. The support for these centers approximates $826,653.

Examples of investigations being carried out in several of the centers will be described. One group is investigating the mass spectrometer on an experimental basis in animals as a means to obtain information regarding cerebral circulation in the presence of severe trauma. Studies have progressed to the point that instrumentation now being developed will make possible the application of the technic for human use. Problems have arisen in the development of a catheter suitable for human use with the mass spectrometer which is vacuum tight so that the entire molecular flow of gas will pass through the membrane. Experiments are under way to modify the intravascular catheter, resolving the apparent difficulties so that the investigations can be pursued in human trauma studies.

Another group reports that a two bed, head trauma unit has been completed for the study of seriously injured patients. Special equipment will make possible the observation of patients for the performance of certain studies, especially those related to blood gases. The relationship of pulmonary function to cerebral function and to recovery or lack of recovery of patients with serious cranio-cerebral injuries will be determined. Other studies are those related to patients who develop hemorrhagic pneumonia. The investigators' experience indicates that, if the pneumonia is not recognized during the first 24 hours after injury, it becomes intractable and often causes death. Severe pulmonary lesions may be present during the first 24 hours after injury and yet the clinical examination may be negative. Existence of the pneumonia has been indicated by determination of pO_2 and pCO_2 but the inadvertant administration of high concentrations of O_2 may cause capillary dilation and increase the tendency to hemorrhagic pneumonia. Alternatively excessive respiratory assistance may eliminate too much CO_2 and convert hypercarbia to hypocarbia. The investigative team proposes to carry out measurements of pulmonary and cardiac function within 24 hours of injury in order to understand the changes that underlie the development of hemmorrhagic pneumonia. This will lead to better methods for monitoring such patients so that optimal administration of O_2 and other therapy may minimize hemorrhagic pneumonia and increase chances of survival. Procedures to be used will include heart catheterization studies, measurement of blood gases, and radiologic methods such as angiography and scanning techniques. Particular attention will be given to measurements of pO_2, pCO_2, cardiac output, pulmonary artery pressure, and pulmonary arteriovenous shunts.

Another interesting study this group has underway is an assessment of the microbiologic flora in patients with head injury in order to determine changes that may occur and to relate changes in flora to the occurrence of clinically recognized secondary infection. To date 21 patients have been studied extensively. Organisms not ordinarily found have been identified,

and their frequency and sources tabulated. In 5 patients, illness was caused by abnormally occurring organisms, and in 10 others, illness from such organisms was suspected. Clinical illnesses included terminal sepsis in one patient and bacterial meningitis in another. By instituting careful procedures, secondary infections were reduced. It is anticipated that, by continuing investigation of sources and causes of secondary infections in patients with head injury, evidence for the need to control secondary infections may lead to significant increases of survival in these patients.

Experimental studies on the neurochemical alterations associated with head injury are continuing, the main emphasis being directed toward, a) chemical alterations in cerebral edema, b) metabolic changes in brain in acute edema, c) plasma and CSF lactate levels following head injury. The first two studies referred to are being carried out in animals, the last one both in animals and man. Methodology has been developed, and experimental studies have been initiated.

Another center is devoting its attention to laboratory and clinical studies of head injury with particular attention to the role of vascular changes in the production of cerebral edema, direct monitoring of intracranial pressure through ventricular drainage, the role of lesions in the region of the hypothalamus in the production of edema, beneficial effects of hemodilution, the use of the hyperbaric chamber in animal studies, as well as a number of other studies.

APPENDIX A

NUMBERS OF RESEARCH GRANTS SUPPORTED
IN FY 1969 AND AMOUNTS ARRANGED BY DISORDER CATEGORY

TYPE OF DISORDER	NO.	AMOUNT	% of $
ALL DISORDERS	1,798	$ 67,775,000	100
1. NEUROLOGICAL DISORDERS			
A. Chronic Neurological Disorders of Childhood	132	3,942,000	5.8
B. Chronic Neurological Disorders of Aging	60	2,371,000	3.5
C. Cerebrovascular Disorders	95	5,407,000	8.0
D. Epilepsy and Related Paroxysmal Disorders	65	2,274,000	3.4
E. Sclerosing Disorders	78	2,797,000	4.1
F. Muscular & Neuromuscular Disorders	152	5,013,000	7.4
G. Infectious Diseases	23	586,000	0.9
H. Accident and Injury	50	1,900,000	2.8
I. Tumors of Nervous System	41	982,000	1.4
J. General	360	12,200,000	18.0
ALL NEUROLOGICAL DISORDERS	1,056	$ 37,472,000	55.3

TYPE OF DISORDER	NO.	AMOUNT	% of $
ALL DISORDERS	1,798	$ 67,775,000	100
1. SENSORY & PERCEPTUAL DISORDERS			
A. Disorders of Vision	413	15,588,000	23.0
1. Cataract	(36)	(1,209,000)	(1.8)
2. Glaucoma	(35)	(1,176,000)	(1.7)
3. Retinopathy & Neurological Mechanism of Vision	(178)	(5,980,000)	(8.8)
4. Inflammatory & Parasitic	(52)	(2,388,000)	(3.5)
5. Metabolic & Degenerative	(14)	(569,000)	(0.8)
6. Strabismus & Neuromuscular	(28)	(941,000)	(1.4)
7. Injuries & Other Disorders including Tumors	(14)	(470,000)	(0.7)
8. General	(56)	(2,855,000)	(4.2)
B. Disorders of Hearing and Equilibrium	165	6,820,000	10.1
C. Disorders of Speech & Other Higher CNS Functions	33	1,991,000	2.9
D. Disorders of Other Senses	87	2,752,000	4.1
ALL SENSORY & PERCEPTUAL DISORDERS	698	$ 27,151,000	40.1
3. MULTI-CATEGORICAL	44	$ 3,152,000	4.6

May 15, 1969

Annual Report
Training Grants and Awards Branch, NINDS
July 1, 1968 through June 30, 1969

The extramural training program of the National Institute of Neurological Diseases and Stroke, formerly NINDB, includes three types of support. All funds are awarded on a competitive basis.

1. Graduate Training Grants provide funds to institutions for the establishment, improvement and support of broad, fundamental training in disciplines related to neurological, neuromuscular, sensory or communicative disorders. The primary objective of the program is to train additional needed clinical and laboratory teachers and investigators and community health and public health personnel. In addition, Special Fellowships (Traineeships) are awarded to provide individual stipend support to clinical and laboratory scientists for advanced, highly specialized research training in preparation for careers in research and academic medicine. Traineeships are awarded also to physicians for specialized clinical training to increase their expertise in the prevention, diagnosis and management of cerebrovascular disease.

2. Through Postdoctoral Fellowships, NINDS provides support to individual clinical and laboratory scientists for research training which follows immediately on receiving the doctoral degree.

3. Career Development Awards provide a substantial period of salary support for the young investigator, either clinical or laboratory, desiring experience and further training in an environment favorable to his establishment as a fully independent investigator and teacher.

NINDS has had primary research and research training responsibility for three broad categories of diseases and disorders--those relating to the central and peripheral nervous system, the communicative system and the visual system. There are, of course, areas of overlap among the three. After FY 1969, responsibility for a large majority of the grants and awards relating to vision will pass to the newly formed NEI.

Although each area has its distinctive training philosophy and needs for trained personnel, and therefore progress will be reported for each separately, certain problems are shared by all three.

The financial support afforded through the NINDS training grant and fellowship programs has played an important, if not essential, role in making it possible to establish an effective core of young basic and clinical scientists well-prepared for research and teaching in each of these three areas of medicine. Modest, but regular, budgetary increases in the past made this development possible.

It is ironic, then, that at the very point in time when manpower available to provide training leadership gives hope for approaching the needs of the next decade across the nation for competent teachers, researchers and physicians, the increases of financial support for training to make this possible have

virtually ceased.

Although in 1969, the Institute supported 310 training programs for a total of $16.929,000 all were supported substantially below the level recommended, and available funds did not allow the renewal of four approved programs nor the initiation of 17 new approved programs. In addition to 211 special fellowships (Traineeships) supported in 1968 for a total of $2,400,000 funds were not available to pay 34.

Postdoctoral Fellowships for $985,000 were awarded to 117 individuals in 1969, but there were 10 approved for whom funds were lacking.

Research Career Development Awards in 1969 were 94 in number for a total amount of $2,258,000, but 33 candidates approved with excellent priorities could not be paid.

Communicative Disorder Research Training

The number of training grants in the field of otolaryngology and in disciplines related to speech, hearing, and communicative disorders was increased by only two in 1969. Five additional approved grants went unfunded, and all 73 grants were funded in substantially lesser amounts than had been recommended, although costs of maintaining excellence in ongoing programs mount every year. Encouraging indications have appeared this year of increasing interest in training for investigative careers in the area of speech disorders, where problems are complex and training must be interdisciplinary.

Neurological Science Research Training

The number of training grants in the broad field of the neurological sciences was increased by only one over those supported in 1968. However, there were 11 new and two renewal approved applications which could not be paid from the funds available. All ongoing programs were paid in amounts reduced drastically from those recommended as reasonable to allow for satisfactory progress.

The trend noted in 1968 toward organizing training in the neurological sciences on an interdisciplinary basis has continued in 1969, with the submission of excellent training proposals embodying fresh, new approaches to the training of investigators and teachers.

Vision

There are three more training programs in the vision field in 1969 than there were in 1968 and an additional five could have been awarded, had the funds been sufficient. In this area also, the Institute was obliged to reduce grants to ongoing programs even below levels currently being received.

There has been a recent upswing in the number of programs which can provide training in ophthalmic pathology, largely because NINDS training grant and fellowship support in the past has increased the number of scientists specially prepared for research and teaching in this important but understaffed area of

vision research. This is the last year that training grants and fellowships in the field of vision will be a part of Institute responsibility. They will be transferred on July 1, 1969, to the new National Eye Institute.

Appendix A

Distribution, by Scientific Fields, of Training Grants Supported in Fiscal Year - 1969

Fields	No.	Amounts
Neurology	73	$ 5,203,000
Ophthalmology	56	3,205,000
Otolaryngology	49	2,864,000
Cerebrovascular	6	185,000
Communicative Disorders	8	362,000
Medical Audiology	9	374,000
Neuroanatomy	6	247,000
Neurobiology	2	40,000
Neurochemistry	2	133,000
Neuropathology	14	629,000
Neuropharmacology	4	232,000
Neurophysiology	13	682,000
Neuroradiology	9	254,000
Neurosurgery	25	888,000
Neurological Basic Science	3	150,000
Ophthalmic Pathology	1	49,000
Otolaryngology & Audiology	2	212,000
Pediatric Neurology	18	727,000
Sensory Physiology - Vision	3	151,000
Sensory Physiology - Oto.	1	20,000
Speech Pathology	3	234,000
Speech Pathology & Audiology	2	75,000
Vision Psychophysiology	1	8,000
TOTAL	310	$16,929,000

May 15, 1969

Appendix F

Distribution, by Scientific Fields,
of Special Fellowships Awarded in FY 1969

Fields	No.	Amount
Audiology & Speech Pathology	7	$ 91,400
Biophysics	3	41,000
Cerebrovascular	..	43,400
Neuroanatomy	3	36,200
Neurobiology	2	13,200
Neurochemistry	7	96,000
Neuroendocrinology	2	26,400
Neurology	12	159,700
Neuropathology	21	216,500
Neuropharmacology	2	27,000
Neurophysiology	21	224,700
Neuroradiology	19	221,300
Neurosurgery	..	49,200
Neurovirology	3	37,400
Ophthalmology	30	397,000
Otolaryngology	..	47,500
Pediatric Neurology	43	136,600
Physiological Psychology	4	29,400
Sens. Physiology - Vision	2	14,000
TOTAL	211	$2,400,000

May 15, 1969

Appendix C

Distribution, by Scientific Fields, of Fellowships Awarded in FY 1969

Fields	Research Career Awards		Research Career Development Awards		Postdoctoral Fellowships	
	No.	Amount	No.	Amount	No.	Amount
Audiology	1	$29,700	5	$112,700	-	----
Cerebrovascular	1	30,000	2	44,500	-	----
Neuroanatomy	2	43,100	1	17,800	6	48,000
Neurobiology	-	----	-	----	3	26,500
Neurochemistry	1	31,800	10	241,900	12	96,000
Neurocytology	-	----	4	86,500	7	61,000
Neuroendocrinology	1	26,000	-	----	4	29,700
Neurology	2	61,800	4	106,400	10	94,500
Neuropathology	-	----	6	141,300	3	24,000
Neuropharmacology	2	58,600	9	208,300	7	61,000
Neurophysiology	1	30,500	26	613,200	31	254,700
Neurosurgery	-	----	-	----	4	30,000
Neurovirology	-	----	3	65,800	2	16,900
Otolaryngology	1	32,400	-	----	1	10,000
Ophthalmic Pathology	-	----	3	67,000	3	26,000
Ophthalmology	1	32,400	5	152,300	8	70,300
Physiological Psychology	1	27,700	4	126,400	3	26,000
Sensory Physiol. - Vision	-	----	9	198,300	6	53,600
Sensory Physiol. - Oto.	-	----	3	75,600	5	40,000
Speech Pathology	-	----	-	----	2	16,800
TOTAL	14	$404,000	94	$2,258,000	117	$985,000

May 15, 1969

Annual Report
Associate Director's Report
July 1, 1968 through June 30, 1969
Extramural Programs
National Institute of Neurological Diseases and Stroke

The details of mission accomplishment of the Institute's Extramural Research and Training Program, as well as the specific problems associated therewith are included in the reports of the responsible Extramural Program Branch Chiefs. In broader administrative and scientific terms, however, the NINDS Extramural Programs for Fiscal Year 1969 have been characterized by:

A. An improvement in providing the required professional and administrative framework for the encouragement and support of research and training central to the mission of the Institute but yet responsive to the needs of the scientific community. A great deal of staff effort and time has been devoted to defining on an operating level the fine but critically important differentials between (1) mission-oriented directed research and the necessary non-directed, but mission-oriented growth of the neurological, visual, and communicative sciences and (2) providing for adequate stewardship of public funds yet avoiding administrative procedures which are burdensome to grantees and only of secondary importance to good management practices. The success of these efforts is dependent upon a continuing inter-action between the professional and administrative members of the staff and between the staff and representatives of the scientific community. This interchange has flourished during Fiscal Year 1969 and has been characterized by its constructive consequences. Reports from our advisory groups, consultants and grantees strongly support the Institute's philosophical approaches to program development and program management. A reorganization of the Research Grants Branch has helped provide a stronger base for this. In both the Research and Training Programs, the principles of organization focus upon the concepts of (1) each grant having a single manager responsible for both the professional and administrative aspects of the award, (2) each member of the staff being responsible for the development of broad disciplinary areas of research or training (e.g.: clinical neurology, basic neurosciences, human communications, etc.), and (3) specific members of the staff assigned to selected special areas of NINDS mission in accordance with scientific opportunity, program need, and staff skill (e.g.: L-DOPA, Stroke, Cerebral Death, Aphasia, Diabetic Retinopathy, etc.). This has provided a stable framework for the continuing, detailed operations of ongoing programs and the opportunity for special effort in selected areas of program responsibility.

B. A continuing increase in Extramural Program professional and administrative responsibility with an associated decrease in staff size and flexibility. The year has been characterized by additional increases in both the need for detailed professional decision making and grant negotiations and a steadily increasing number of managerial requirements originated by the Department of HEW and the NIH; concurrent with this assigned increase in responsibility and administrative procedure has been an eroding away of staff size and morale through personnel restrictions and minimally adequate personnel management practices; some examples of the latter include long delays in personnel

actions, lack of periodic reports on pending personnel requests, and the using of patterns of organization rather than the level of staff responsibility in the assessment of grade levels. The combination of decreasing staff morale and increasing responsibility poses serious threats to an operation whose administrative standards are those of excellence, and presents the danger of its conversion to one which will be satisfied with levels of performance that are minimal but adequate. Because of this alarming situation, Extramural Programs is faced with the need to develop methods by which the Institute can both discontinue specific Extramural Programs and decrease selected administrative operations of a non-legal variety.

C. A substantial deficit in required research and training funds, the latter being of such consequence that a complete reassessment and redesign of the Institute's Training Programs for Fiscal Year 1970 becomes essential. In both the Research and Training Grant Programs in Fiscal Year 1969, reductions in every grantees' budget were individually negotiated to a level at which further reduction in Fiscal Year 1970 would mitigate against the feasibility of attaining the grant's objectives. Because of this and a critical need to initiate selected new activities of high program relevance, a reassessment of Institute grant objectives and methods has been initiated. This is particularly true in the training area where factors need to be weighed such as the relative needs for additional academic and research personnel in the clinical sciences versus preclinical sciences; the relative importance of support of the training environment versus support of the trainee and the most appropriate administrative instruments of award in each area; the appropriate levels of trainee or fellowship stipend and the relative responsibilities of the training institution and NINDS in providing for these; and the point in a trainee's career when "career development" stability is most critical and productive. In addition, select committees of NINDS consultants are reviewing the national status of specialized clinical training, clinical personnel requirements for providing urgently needed patient care, and the role of the Federal establishment in providing for specialized clinical training.

D. Staff discussion and the preparation of an Institute position in regard to the over-all goals of the NINDS for the decade of the 1970's, particularly as these goals related to problems of clinical trials and to the development and evaluation of controlled community clinical demonstration and evaluation activities. In selected areas of national need, for example, trauma to the brain and spinal cord, the Extramural staff is exploring the feasibility of establishing carefully structured national centers of excellence for research, teaching and patient care as national models for community or regional action. In such national centers of excellence the differential among clinical research, teaching and patient care can be kept to an absolute minimum and a comprehensive program aimed at the total medical problem of the handling of the acute lesion of life threatening consequence and the prevention of permanent damage. It has been proposed that this "National Models Program" be launched on a pilot basis in selected problem areas such as trauma to the brain and spinal cord, epilepsy, and stroke; it would complement the NINDS active research project, clinical center and training programs in these same areas.

E. Selected areas of program responsibility have been given special attention, including (1) L-DOPA: Upon advice of an NIH panel of scientific experts, the Institute did not move forward with a prospective controlled evaluation of the efficacy and human toxicity of L-DOPA in the treatment of Parkinsomism. A retrospective analysis of available data indicated that L-DOPA probably was clinically efficacious, showed varying degrees of toxicity, and that the known adverse reactions were probably medically manageable. Two corporations in the pharmaceutical industry have launched clinical trials of the chemical in preparation for the submission of an N.D.A. to the Food and Drug Administration. The Institute is observing these trials, initiating selected studies of its own in areas not being adequately explored by the scientific community, developing 4-5 centers of research excellence for long-term studies of basal ganglia and extra pyramidal disease and its treatment through clinical center awards, and organizing workshops on specific scientific and medical aspects of biogenic amines and the nervous system; (2) stroke: having initiated 19 cerebrovascular clinical research centers through its clinical center and specialized research center programs, the Institute has now begun to select those centers in which long-term clinical research and laboratory efforts have the highest probability of success, and will discontinue the others. This "weeding out" process will take approximately two years at the conclusion of which up to ten clinical research centers will remain and serve as national focal points for research and training on problems of the cerebrovascular diseases; (3) human communication: a three-year effort has been completed in which the total national problem of human communication and its disorders has been assessed and a comprehensive report prepared describing the state of this national problem, the present efforts being taken to meet these needs, and plans for meeting them; appropriate parts of the report will be published and distributed. Using this report as a working document, the Institute will evaluate its own efforts in this program area and initiate selected additional activities as staff, funds, and opportunity permit; (4) visual disorders: retrolental fibroplasia, a previously major cause of blindness in the USA, has begun to reappear as a result of oxygen therapy of the acute respiratory distress snydromes of the premature. The Institute has initiated a cooperative study to develop methods by which blood oxygen tensions can be measured more precisely in clinical situations and more exacting standards of oxygen therapy established which will provide for metabolic needs but still be below dangerous levels of visual development. Also, because of the unsatisfactory status of therapy for diabetic retinopathy, the NINDS has inaugurated a cooperative study to evaluate the efficacy of presently available methods of therapy.

F. Staff reorganization and operational modernization. A formal reorganization of the professional and managerial staff of the Extramural Programs has been completed in order to provide for greater identification and authority where responsibility for program operation exists. As part of this, the Research Grants Branch has been sectionized and within each Section staff scientists designated in the areas of the basic neurological sciences, the clinical neurological sciences and the communicative sciences; the same designations occur in the training areas. Despite this reorganization, the principle of a single staff scientist having total responsibility for all professional and managerial decisions on any particular grant has been maintained. Also, the

operations of the data reports and analysis section, OAD, have been reorganized to provide for conversion of a marginal punch card data storage and retrieval system to one utilizing the computer facilities of both the DCRT and DRG. This will provide for greater efficiency of operation but at the cost of less flexibility in data management; these latter compromises are the result of restrictions on the recruitment of necessary technical and clerical staff.

G. The initiation of the activities of the National Eye Institute. A National Advisory Eye Council has been appointed, an orientation and planning meeting held in March 1969 and a regular meeting held in June 1969. In addition, with the assistance and cooperation of the DRG, the philosophical and operational dissection of the grant and award programs of the NINDB into the NINDS and NEI has been completed. During Fiscal Year 1969, the Extramural Program staff of the NINDS continued to carry all responsibilities for NEI grant and award programs. Because of the continuing attrition of personnel, however, the over-all percentage of NINDS staff time available for this has decreased and continues to grow less. In Fiscal Year 1970, the staff of NINDS plans to assist the newly designated staff of the NEI in a supportive role, instead of as the responsible agents of the new Institute. The techniques and guidelines for this have been developed and are now operational.

Annual Report
July 1, 1968 through June 30, 1969
Research Grants Branch
National Institute of Neurological Diseases and Stroke

Introduction

The name of the Institute has been changed twice during the past year. With the legal authorization for the establishment of a National Eye Institute on August 16, 1968 the name was changed to National Institute for Neurological Diseases. It was later changed to National Institute of Neurological Diseases and Stroke. However, these changes have not affected the mission or activities of the Research Grants Branch in that the research grant programs of the NEI have continued to be the responsibility of the Branch during FY 69.

The scientific approaches to, and the scientific advances made in the various disorder categories within the mission of NINDS are summarized in subsequent sections of this Report. Therefore, comments here are limited to a few generalizations pertaining to both scientific and administrative aspects.

About a year ago data became available from several investigators, most of whom were supported by NINDS, to indicate that L-Dopa (3, 4-dihydroxyphenylalanine) might be highly effective in the treatment of Parkinson's Disease. These preliminary data indicated that at least 50% of the patients showed remarkable improvement and another 25% showed appreciable improvement. Even though the doses were large and serious toxicity would occasionally develop, the therapeutic potential of L-Dopa was considered very important. A proposed cooperative study of 20 institutions to evaluate this therapy was disapproved by expert consultants with the hope that data already available might answer the major clinical questions of efficacy and toxicity. This turned out not to be the case. Further review of the situation indicated that studies already supported by commercial pharmaceutical firms to satisfy FDA requirements plus projects presently supported by NINDS and other agencies would soon provide needed clinical data without further support from NINDS. Perhaps the most important needs for the future are 1) the synthesis and testing of one or more analogues or potentials of L-Dopa which will be more effective with less toxicity and 2) the additional insight into the chemistry and metabolism of the brain.

Research supported by this Institute virtually eliminated retrolental fibroplasia by the discovery in the early 1950's that it was usually caused by the exposure of infants to high oxygen concentrations. The more recent use of oxygen for hyaline membrane disease and other respiratory distress syndromes in infants has reopened the whole problem. Investigators at five institutions have just begun a two year cooperative study to establish safe guidelines for oxygen therapy in the premature infant.

There is considerable concern about the increasing incidence of diabetic retinopathy and the lack of a really satisfactory treatment. The NANDS Council has recommended support for a Planning Committee on Diabetic Retinopathy to 1) review the literature 2) identify research needs in the natural history and therapy of the disease and 3) develop an experimental animal analogue. Support has also been provided for a series of three workshops over five years to explore the development of studies on specific aspects of diabetic retinopathy.

After several years of work, the NANDS ad hoc Subcommittee on Human Communications and Its Disorders has submitted a three-volume report with twenty-six specific recommendations. The report includes a detailed analysis of the present state of research and training in this area. The recommendations are presently under review by the Council. Their implementation would increase research and research training in Human Communications by about 100% during the next five years.

The NANDS ad hoc Subcommittee on Rehabilitation also has submitted an extensive report on problems of blindness rehabilitation; this report is under review by the newly established National Advisory Eye Council. The work is concerned with the concentrated application of systems analysis and conceptual models to the study of blindness and services to the blind in the United States.

A new administrative problem this year was the negotiated reduction of every research grant, competing or committed, in order to have funds to award a reasonable number of new and renewal grants. All grants were individually negotiated downward by an amount which would still allow the work to proceed, although productivity was unquestionably reduced.

The Research Grants Branch was fortunate in maintaining a stable and experienced staff during the year. The transfer to the National Eye Institute of work on vision and its disorders will result in the loss of one professional staff member and will lead to an increased work load for all other members of the staff, because the one staff member has been responsible also for several areas other than vision. Because of increased activity in the Special Programs, some research project responsibilities from that area will have to be reassigned. These changes will require that the staff member lost because of the transfer to the NEI be replaced as soon as possible.

This year 1,798 research grants were supported at a total cost of $67.8 million. Last year the comparable figures were 1,780 grants for $65.1 million. The numbers of grants and amounts of funds in the various disorder categories are shown in Appendix A.

COMMUNICATIVE DISORDERS

Progress in research in the communicative sciences supported by the National Institute of Neurological Diseases and Stroke has been highlighted by many valuable contributions to the general understanding of the underlying mechanisms and dynamics of normal human communication and the several diseases which impair it.

Sensory Processes

In the area of sensory processes one investigator reported three major accomplishments. Work progressed on 1) the determination of a general decay time constant in the peripheral and low central auditory system 2) determination of the acoustic impedance at the human eardrum up to a sound frequency of 7000 Hz and 3) determination of subjective vibrotactile intensity as a function of vibration amplitude and frequency. Investigations of central auditory masking and comparison of their results with neurophysiological recordings have shown that single neurons as well as groups of neurons of the 8th nerve, the cochlear nucleus, and the superior olivary complex fire at a rate which is maximum near the onset of stimulation and decays exponentially with a time constant of about 50 milliseconds. The decay time constant, as derived from central masking and neural recordings, appears independent of stimulus and of the tonotopic location. The invariance of the time constant with the neural level and its direct reflection in a behavioral response strengthens the evidence for the linearity of the central auditory system.

Inner Ear

The ears of seven chinchillas with complete section of the tract were examined by electron microscopy, along with normal animals. Results show that the outer hair cells are supplied for the most part (although not completely), by the crossed efferents, whereas the homolateral efferents are restricted to the inner spiral and tunnel bundles. Input-output function for cochlear microphonics as well as whole nerve action potentials, were measured at 1000 Hz in the ears of three animals at 14, 17, and 96 days after tract section. Responses were also measured in three animals just before and after tract section. Some differences in response before and after tract section were present, but these were no greater than variations encountered among normal ears. An endolymphatic hydrops experiment involving a light microscopic study of guinea pig inner ears operated upon for blockage of the endolymphatic duct and sac has been completed. The essential findings were the presence of hydrops in all sixty-one operated animals and frequent demonstration of lesions in the sensory cells, spiral ganglia and stria vascularis at the apical turn of the cochlea; the vestibular neurosensory elements remained essentially unchanged. None of the control animals showed hydrops.

Hearing

Electrophysiological experiments on cats with several electrodes permanently implanted within the cochlea suggest that it is becoming reasonably certain that some types of deafness related to cochlear defects are at least within the realm of surgical therapy. Twenty-four chinchillas have been exposed to a series of moderate intensity noise. Results indicate that although group means were stable from week to week when the same noise exposure was used, individual values of temporary threshold shifts (TTS) varied greatly. The noise was increased to 124 dB SPL. A two-hour exposure at this intensity produced permanent threshold shift (PTS). Analysis revealed none of the tests of TTS, the presumed predicator of PTS, showed significant correlations with the final PTS. In another series of studies on loudness, one researcher reported that the Physical Correlate Theory applied to loudness judgements considers that twice subjective levels of self-generated (autophonic) sounds are equivalent to estimates of the increase in sound level required to project ones voice twice distance. The Physical Correlate Theory considers that subjective magnitude judgements of both distance senses, vision and hearing, are based upon experience with changes in distance. In utilizing a new technique involving intracellular recording on the isolated spinal cord of the frog, an investigator was able to determine whether in the central nervous system there occurred a natural spontaneous release of transmitter from the presynaptic terminals. There had been conflicting evidence concerning the origin of so called "synaptic noise". The investigator showed that after all elicited impulses were blocked by tetrodotoxin, miniature synaptic potentials could still be recorded at rates not significantly different from those before the administration of the drug. These results suggest that in the isolated spinal cord of the frog, the miniature synaptic potentials were analogous to miniature end-plate potentials at the neuromuscular junction.

Hearing Disorders

Work is proceeding in establishing norms for the various parameters of human stapedial and tensor tympani reflex actions in normal populations and to compare results in patients with various middle ear pathologies. The method employed uses both impedance audiometry and typano-manometry. Electrodermal audiometry has aided in resolving the controversial question concerning hearing impairment associated with Rh incompatibility. Results of this study strongly indicate lesions low in the central auditory nervous system (cochlear nuclei) or in the peripheral sensory-neural mechanism (cochlea), not at high levels in the central auditory system. This localization of damage is an important step in understanding the nature of the impairment and in facilitating more effective aid to the individual. Significant damage to the organ of Corti was found to occur when chloramphenicol was experimentally appled to the middle ear in a large number of guinea pigs. The study was conducted to histologically evaluate and localize damage resulting from the direct application of chloramphenicol to the window of the middle ear. Wide spectrum chloramphenicol has been widely used by otologists because of its effectiveness when applied topically

to the middle ear in cases of chronic refactory otitis media and following typanomastoid operations. The histologic results indicated that chloramphenicol used in this way produced hearing loss through extensive damage to the organ of Corti and variable damage to the stria vascularis in the basilar turn of the cochlea. These findings should alert otologists to the danger of using chloramphenicol topically in the middle ear.

Bone Banks

In one Temporal Bone Pathology Laboratory, a total of 67 pairs of human temporal bones were received within the first six months. In almost every instance the brain was collected simultaneously. These brains are prepared for histologic study in the Neuro-pathology Laboratory. The anatomical material collected from these various sources represent a broad variety of valuable pathology which in every instance involves cochlear and vestibular system or other structures of the temporal bone.

Comparative Hearing

Further work is continuing on the structure and function of the ears of lower vertebrates especially the lizard. The results will extend our understanding of the relations between the details of structure and performance of these ears as shown by cochlear potentials. These results will also provide a better estimation of the degree to which different lizard species have developed pitch discrimination in terms of place representation along the basilar membrane. In an investigation of the function of the round window in the frog, evidence has been obtained by blocking this window that it serves as a yielding point in the action of sound pressures on the inner ear, just as it does in the higher vertebrates. Substantial progress has been made in studies of the use of echolocation by bats in the location and identification of objects. This manner of object perception is being analyzed in an effort to determine the particular acoustic cues utilized by the bat in different situations. It has been found and verified that the bat used temporal information in the discrimination of distances.

Hearing and Heredity

In experimental studies in hereditary deafness, 125 patients in 35 families have thus far been examined in a hereditary deafness clinic. Three families with dominantly inherited low frequency hearing loss have been identified and special audiologic testing has permitted a clear delineation of this newly recognized genetic entity. In addition, several patients with unusual chromosome anomalies have been examined, resulting in a definite description of laryngeal abnormalities in the Cri-du-Chat syndrome. A new syndrome of cochlear deafness, high myopia, and intellectual impairment is presented. Four of seven siblings are affected in an inbred Amish family, indicating a simple autosomal recessive mode of inheritance. None of the mentally unaffected siblings are myopic or have hearing problems.

Speech

In otolaryngology and speech pathology one researcher pointed out that to understand and provide rational therapy for phonatory voice disorders, it is necessary to understand the behavior of the larynx during the production of both normal and abnormal vocal sound. Analysis of ultra high speed motion pictures of larynges supports the hypothesis that there are at least four types of normal laryngeal behavior employed in speaking: 1) open larynx, no vibration 2) closed larynx, no vibration 3) incomplete closure during phonation and 4) complete glottal closure during vibration. Analysis also reveals that the vocal cords are capable of independent vibration and are influenced by unilateral disease or other conditions. Differences in vibrational pattern between the two vocal cords causes rougher sounding voice when the composite vibration creates random irregular variations in the sound wave. In a study of aphasia, speech patterns were found to correlate with anatomical lesions. The study suggests the presence of two distinct types of aphasia occuring with sufficient frequency to warrant consideration as syndromes. Actually, it was shown that a large percentage of aphasics can be placed in one of the two groups on the basis of speech characteristics alone and that the causative lesions producing these distinctive groups arise from separate anatomic localizations. The anterior area appears capable of producing cliche type, over-learned speech patterns while the posterior area is necessary for the specific exact use of language. In 100 patients with aphasic syndrome, a lesion located anterior to the Fissure of Rolando (the speech area of the frontal lobe) was associated with low verbal output, dysprosody, dyscertheria, considerable effort and predominant use of substantive words; whereas posterior lesions (the speech areas of the parietal and temporal cortex) showed little effect on these features but resulted in paraphasia, press of speech, and lack of substantive words.

Antiviral Substances in The Cornea

Since the discovery of the first therapeutically active antiviral compound, IDU, its potency in treating experimental herpes simplex has been well documented by many researchers, and the effectiveness of the drug in man has been established in five double blind studies. The Food and Drug Administration has accepted it and it is now widely used clinically. The ability of corticosteroids to suppress herpetic stromal edema has been established and IDU can inhibit the deleterious effects of corticosteroids on epithelial disease.

The shortcomings of the drug have also become apparent. Its effective therapeutic concentration is limited by poor solubility, and the use of special non-aqueous solvents such as DMSO are of little help in increasing therapeutic efficacy. In addition to limited concentration, resistance (in tissue culture) develops rapidly. Although the drug can be given parenterally and has apparently saved the lives of several children with herpes simplex encephalitis, it is a poor drug for systemic administration. It is hydrolyzed rapidly and may alter the chromosomal patterns so that its use in only potentially fatal diseases seems justified.

In order to find better drugs, the correlation has been studied between tissue culture activity and *in vivo* activity against corneal disease. A precise double blind evaluation system for *in vivo* measurement of activity utilizing herpetic corneal ulcers has been developed. This allows one to relate the improvement in corneal disease due to treatment to the concentration of the compound in eye drops and to plot precise, reproducible dose-response curves. For the first time this allows a quantitative evaluation of the potency of topical anti-viral compounds (a type of ED50), the determination of meaningful therapeutic-toxic ratios, and the precise comparison of drugs in terms of attainable antiviral activity. The tools to permit a precise evaluation of antiviral drugs *in vivo*, and this system with IDU as the positive control, is now a standard system used by most drug companies studying antiviral drugs. It has also permitted an *in vivo* study of metabolic rate-limiting steps for antivirals, which is important because these compounds can act at multiple sites. Additive or synergistic antiviral effects can be quantitated as well as competitive and non-competitive reversal of antiviral activity.

With these methods a wide variety of newer anti-metabolites have been discovered. Some, such as cytosine arabinoside, were too toxic to be useful. Others, such as methylamino deoxyuridine. (MADU) lacked potency, but one, 5-trifluoromethyl-2-deoxyuridine (trifluorothymidine or F_3 TdR), was exceedingly potent, with almost no toxicity, and almost no propensity to stimulate resistance to the drug by the virus. In rabbits, it made herpetic ulcers heal rapidly and reliably and the drug was a superior antagonist of the tendency of steroids to make herpes worse.

Glaucoma

Currently the importance of aqueous humor dynamics is undergoing analysis. If the true facility is defined as the increase in outflow of the fluid from the eye with an increase in the intraocular pressure, then pseudofacility is defined as the decrease in the flow of liquid into the eye with an increase in the intraocular pressure. Pseudofacility is affected by the hydrostatic pressure and the colloidal osmotic pressure of the blood within the vessels of the eye, the intraocular pressure and the permeability of the vascular bed. The magnitude of pseudofacility could represent one of the regulatory factors in the maintenance of intraocular pressure. Secondly, total facility (true facility plus pseudofacility) is the value measured by tonography. Subtracting the value of pseudofacility from total facility, yields true facility (outflow via Schlemm's canal). The first determination of pseudofacility in the eye of man has recently been reported. Pseudofacility was 20% of the total facility or 0.06 ul/min/mmHg.

Visual Electrophysiology

Recent investigations indicate that the Electrically Evoked Response (EER), a technique for recording the occipital response to electrical stimulation of the globe of the eye, represents a new type of measurement promising potentially useful information on visual function. It is one of several types of stimuli other than visible light used by investigators to create the sensation of light.

Both EER and the Visually Evoked Response (VER) have been useful in studying the eye. Results of the present investigations show that the EER is a distinct and separate entity from VER, utilizing part of the same pathways as the VER but differing in several notable respects. There is measurably shorter latency of the EER than the VER of the same subjective brightness, which suggests that at least one step in the retinal transmission chain has been bypassed--the rod outer segment step, or possibly the whole receptor--with the bipolar or ganglion cells stimulated. Differences in amplitudes of EER and VER of the same subjective brightness were found. The non-selective electrical stimulus appears to activate in a nonspecific way many cell trains (collateral circuits) which do not contribute to the sensation of brightness. These noncontributory circuits seem to terminate their activity in the occipital region.

In EER, the investigators sum the responses to repeated stimuli on a small special computer which permits recordings from the scalp of the intact human being. The stimuli are induced through a low vacuum contact electrode (the active electrode) and a U-shaped silver foil electrode (the inactive electrode) applied to the periorbital skin. Although there is considerable variation of EER from individual to individual, the response for any one subject appears to be constant.

The investigators report that these preliminary investigations are being expanded to include more standardization studies and investigations of disease involving retinal disorders. Expansion of investigations into EER production by other scientists seems imminent.

Rehabilitation In Eye Disorders

The special problems of prescribing suitable aids for partially sighted children have been under investigation for several years. Findings show clearly that in children with a static level of visual impairment the lens needs re-evaluating at intervals to determine when an increase in power of the reading aid is required. The two principal reasons for the changing requirements are (a) decrease in ability to sustain accommodation for a close reading distance and (b) decrease in the size of the text the child wishes to read.

Retrolental Fibroplasia

Recently high oxygen therapy has been found necessary to save the lives of premature infants who develop respiratory distress. Approximately 40,000 infants need such treatment every year. Nearly 20 years ago work supported by this Institute showed that the excessive use of oxygen therapy in such infants was the principal cause of retrolental fibroplasia which almost invariably results in blindness. Subsequently it was shown that the disorder could be prevented in many cases by constant control of the oxygen concentration in the eyes of infants while under oxygen therapy.

Despite this information there seems to have been a marked increase in the incidence of retrolental fibroplasia since the use of oxygen therapy became justified in the past few years. Many hospitals do not have facilities to monitor arterial oxygen and the levels that are safe for the retina of the premature infant are still unknown. To attack this problem the Institute has just begun to support a cooperative study including investigators at five separate institutions with the objective of establishing safe guidelines for oxygen therapy to the premature infant. The study is designed to (1) develop an improved arterial oxygen tension monitoring device; (2) determine oxygen time-dose relationships to retinal changes; and (3) examine histologically any eyes that may become available at death after exposure to oxygen. It is expected that this study will make important progress in this difficult area in two years.

Neuromuscular Disorders

Myasthenia gravis and the various muscular dystrophies constitute the most prevalent neuromuscular diseases. The dystrophies encompass a large variety of clinical conditions and new dystrophic varients in both humans and animals are described each year. They are usually genetic in origin although dystrophic changes are observed in experimental animals subjected to nutritional deficiencies. On the other hand myasthenia gravis has been recognized as a clinical entity for several hundred years.

The symptoms of myasthenia gravis are related to impaired transmission through the myoneural junction although it has not been established whether the deficiency is prejunctional or postjunctional. In the latter case, it would signify a decreased sensitivity to the transmitter, acetylcholine. If the defect were prejunctional, it would suppose that acetylcholine synthesis or release in response to motor nerve stimulation is impaired. Current therapy is centered around the administration of anticholinesterase agents which decrease the rate of inactivation of acetylcholine at the postjunctional site. While this implies refractoriness of the postjunctional receptors, recent studies of miniature endplate potentials suggest that the sensitivity of the endplate to acetylcholine is unaffected in myasthenia. Identification of the primary cause of the disease may eventually be clarified by the use of guanidine, a drug which facilitates the release of acetylcholine from motor nerve terminals. If the defect resides in acetylcholine release, guanidine should be of dramatic benefit. If the defect is in acetylcholine formation, initial improvement should be followed by deterioration of transmission as stores are depleted. Results thus far indicate that guanidine may be of benefit to some patients while others are adversely affected. Tentatively, some investigators now conclude that the disease probably does not arise from impaired release of the neurohumor. However, the nature of the physiological defect may vary from one patient to another or with the severity of the disease.

Recent research has suggested that myasthenia gravis may be an autoimmune disease. Lymphoid hyperplasia of the thymus occurs in approximately two-thirds of all patients and occasionally thymectomy induces remission. The immunoglobulin fraction of the serum of some patients binds with the cross striations of skeletal muscle. Serum globulins from patients may also react with the nuclei of various cells, cytoplasm of the epithelial cells of the thymus, and ribonucleoprotein of skeletal muscle. The striations of skeletal muscle obtained by biopsy contained globulin in some patients, and globulin was found in the skeletal muscles of rats following intraarterial injection of the serum of myasthenic patients. According to this theory of the etiology of myasthenia gravis, the neuromuscular junction of patients is believed to be sensitive to a circulating neuromuscular blocking agent. However, efforts to directly test this idea by the administration of myasthenic serum into rats has led to conflicting results.

The muscular dystrophies have been variously associated with morphological, chemical or physiological changes in muscle, nerve, the circulation or the myoneural junction. A variety of animal dystrophies are available for experimental laboratory use. The various clinical entities observed in humans are classified mainly by histological and histochemical analysis of biopsy material. Much research in this area is concerned with the correlation of histology with electrophysiology of nerve and muscle, chemical analysis for the activities of various enzymes and alterations observed with the electron microscope.

Recently studies of the chemistry and structure of human actin and myosin have begun. Since these are the predominant proteins of muscle, detailed information of this nature may eventually prove of value in tracing the etiologies of various dystrophies via the pathways of protein synthesis.

A careful and detailed protocol for the evaluation of therapy in muscular dystrophy has been developed and is currently employed in two centers to assess the possible therapeutic effects of hexahydrocoenzyme Q_4 on the course of dystrophy of the Duchenne type. This material was found to be effective in the treatment of the genetic muscular dystrophy of the Bar Harbor strain 129 mouse. The substance is a derivative of coenzyme Q_{10}, reported useful in the treatment of Vitamin E deficiency myopathy in rabbits and hamsters.

Potentially important observation of the effects of a high oxygen environment on the early course of genetic muscular dystrophy in chickens has been reported. Exposure to a 70 percent oxygen environment allowed enzyme development in the microvasculature and breast muscle to procede at a higher rate in affected chicks for the first weeks after hatching. However, the effect was absent after eight weeks of continuous exposure to high oxygen. At all times a direct correlation was observed between enzyme activity of the blood vessels and morphology of the muscle fibers.

Neoplastic Disease

A variety of procedures are employed for the diagnosis of brain tumors reflecting the absence of a standardized, reliable methodology for this purpose. This results from the heterogeneity of brain tumors in terms of size, morphology, vascularity, and metabolic characteristics. The technique used is usually dependent on the training and experience of the clinician. Careful examination of the electroencephalogram taken together with the presenting neurological signs are often sufficient to both diagnose and localize certain tumors. Angiography, x-ray visualization of radiopaque substances injected into the major arteries traveling to the brain, is currently utilized extensively. Its efficacy is based on the rate and extent of filling of the cerebral vasculature and the appearance of abnormal blood vessels. The procedure is not without risk, since the materials injected are potentially neurotoxic if not quickly flushed out of the cranial vessels, or if used in high concentrations. Current research is oriented toward reducing the toxicity of these radiopaque materials by chemical modification of the molecule and by using diluents which retard movement of material out of the blood vessel into the parenchyma.

Tumors which selectively accumulate radioactive tracers may be localized by external scanning. In this instance, it must be assumed that the blood-brain barrier in the affected area has been modified to differentially allow influx of labeled molecules. However, a growing tumor often produced edematous tissue changes in the surrounding parenchyma, including modification of the blood-brain barrier. In these instances radiotracers may enter the brain and delineate the periphery of the malignancy. Human serum albumin iodinated with I^{131} or I^{125} which is maintained in the blood relatively long periods may be utilized for localization purposes under these two circumstances where blood-brain barrier modifications have been produced.

The metabolic characteristics of certain tumors may be utilized for diagnosis. Neuroblastomas synthesize catecholamines at a high rate and this is reflected in the urine by the presence of relatively large amounts of catecholamine metabolites. A potentially important method of diagnosis currently undergoing development is based on the observation that brain tumors synthesize cholesterol actively. When cholesterol synthesis is blocked by the administration of triparanol, a metabolic intermediate, desmosterol, appears in the cerebrospinal fluid. Using clinically standardized procedures for the administration of triparanol and the sampling of cerebrospinal fluid, the increment of desmosterol observed identified 80% of tumors and no "false positives" are found. It should be noted that this method may be used to follow the course of tumor regression following therapy and to check for regrowth or the presence of metastases.

Brain tumors are usually treated by surgery and/or radiation. Often these procedures are palliative in nature since vital brain centers necessary for life may be involved and cannot be extirpated or further damaged. However, progress has been made in increasing the effectiveness of clinical techniques. Recent observations indicate that concomitant treatment with radiation and adrenocortical steroids increases comfort and prolongs life. Tumor regression has also been accomplished by surgical implantation of small radon pellets. Chemotherapy is not extensively used since agents effective in other organs generally cannot pass the blood-brain barrier. In certain instances the barrier is modified either within or around the neoplasm so that it may eventually be possible to administer effective compounds through the cerebral blood supply provided that systemic toxicity is minimized by dilution or isolation of the circulation. Cytotoxic agents placed directly in the cerebrospinal fluid have been effective in controlling meningeal leukemia, but solid tumors have not yielded to this approach as yet.

The incidence of tumors of the nervous system has recently been reported for the entire population of Israel for the years 1961 through 1965. The overall figure of 12.8 per 100,000 is similar to that observed in Sweden and the United States. However, for immigrants of European origin the incidence was 15.6 in contrast to 7.3 for immigrants from Africa. Gliomas accounted for approximately one-third of all histologically verified tumors and meningiomas for about one-fourth. The five year survival rates were 63% for the latter and only 21% for gliomas.

The cause of tumor formation is not known although evidence for a viral origin has been accumulating in the case of experimental animals. It is therefore of extreme interest that a cell free preparation of an experimental animal glioma has recently been shown to be capable of inducing tumor formation in hamsters. Furthermore, virus particles were identified in the precancerous tissue. It is obviously necessary to demonstrate unequivocally that the particles seen were actually viral in nature and that they were causally related to tumor development.

Multiple Sclerosis

A nationwide cooperative study beginning in April 1965 and involving ten University-based treatment centers has treated 197 hospitalized multiple sclerosis patients in acute exacerbation with ACTH and placebo by a double-blind technique under a strict protocol. Five methods of examination and evaluation were carried out before and at weekly intervals for a total of five weeks. Data on the multiple variables of each method were collected and analyzed by computer. A summary of the results shows that with appropriate randomization of patients and treatment, a therapeutic agent can be reliably evaluated in this disease. Careful analysis of data confirms the clinical impression that ACTH has a weak therapeutic effect, somewhat superior to placebo, detectable at the second and third weeks, but which is less definite at the fourth week following the beginning of treatment. Six to eight month follow up observations are not sufficient to provide significant information to determine the late effects.

Experimental Allergic Encephalomyelitis

The demyelinating effect of sera obtained from animals with experimental allergic encephalomyelitis (EAE) has previously been demonstrated in tissue culture. The use of this in vitro model system has been extended to a study of both lymphoid cells and serum samples from inoculated animals. Lymphoid cells were obtained from Lewis strain rats inoculated with either whole bovine white matter in complete Freund's adjuvant or with adjuvant alone. The lymphocytes thus obtained were included in the culture's nutrient medium. Simultaneously, the serum from the same animal was also included in the sister cultures: all cultures were then observed for possible demyelination. The following observations have been made: 1) both lymphoid cells and serum from an EAE inoculated animal produce demyelination in cultured cerebellum and spinal cord. Neither induced demyelination in cultured dorsal root ganglion from peripheral nerve 2) the reaction to cells and serum differ. The demyelinating reaction to serum is rapid, frequently beginning and completing its course within hours whereas the same pattern of change requires days to be completed after exposure to cells 3) preliminary experiments show that washed lymphoid cells maintained in an isolated culture, i.e., in the absence of nerve tissue, release demyelinating substances (antibodies) into their nutrient medium which then cannot produce demyelination in cultured nerve tissue.

Findings which help to explain why myelination takes place in some situations and fails in others and why synaptic connections are re-established on occasion have resulted from an extensive study of the development and myelination in culture of immature cerebellar tissue of the new born mouse. The evidence presented indicates an in vitro persistence of basic affinities between neuronal types. The results also suggest that juxtaposition may enhance myelinogenesis by increasing the number of potential contacts between Purkinje and other neurons.

The cerebellum from the new born mouse was used for study because it is extremely immature at birth and remains myelinated in vitro and in vivo for the first five to six post-natal days.

Cerebellar explants were placed either widely separated or in contiguous pairs. A striking difference in pattern of myelinogenesis and organization was apparent between single and contiguous explants. At 14 days only 14% of single explants were heavily myelinated as compared with 55% of those paired at random, and 86% of those in topographic continuity. It appears that the selective affinities between certain cells of the cerebellar cortex with which they might normally interact in vivo may influence and direct axonal regeneration leading to the re-establishment of synaptic relationships between contiguous explants.

A transient little known type of mononuclear white cell in the peripheral blood has been shown to synthesize a factor capable of breaking down myelin in experimental allergic encephalomyelitis (EAE). It has been postulated that this might also be involved in human demyelinating disorders such as multiple sclerosis. These sensitized cells (immunocytes) reproduced rapidly and demyelination was observed in cultures to begin within a few days after immunization, well before lesions appear in the central nervous system. This has broad implications in studying events preceeding demyelination in a wide range of autoimmune diseases. Utilizing cultures of these circulating immunocytes should allow intensive study of short term in vitro protein synthesis, circumventing the problem of binding action to target organs.

A rapidly increased percentage of monocytes undergoing DNA synthesis was revealed during the inductive phase of EAE by a morphologic study of peripheral blood smears. It was found that these cells usually occur in maxium numbers several days before the onset of CNS symptoms, and were virtually absent by the first clinical evidence of neurologic disease. Many of these cells were found to have an unusually high rate of metabolic activity, releasing substantial amounts of radio-active protein into the supernatent obtained by centrifuging the immunocytes. The presence of the immunocytes may be a signal of immune response of diagnostic value.

Amyotrophic Lateral Sclerosis

An endemic focus of amyotrophic lateral sclerosis (ALS) in the Kii Peninsula in Japan has been under investigation for some time. Included are epidemiologic, genetic, clinical, pathologic, histochemical and trace metal studies.

In the Mitogawa area of the Kii Peninsula a high frequency of motor-neuron disease has now been documented from fatality statistics and epidemiologic survey. Prevalence of ALS (a spinal muscular atrophy) is about one per thousand population, and of primary lateral sclerosis about two per thousand--both far in excess of that found in western countries or in other parts of Japan.

Mortality statistics reveal that ALS was responsible for 71 deaths out of 1,414 deaths in Kii area for the past [illegible] years. This is 10 times the average of the whole of Japan.

Though originally considered genetic, the Marianas form of ALS is now thought to be an exogenous disorder because of 1) discovery of the Parkinsonism dementia complex in these islands; 2) clinical and especially pathologic factors of both ALS and Parkinson's Disease in at least some instances of either entity 3) high frequency of ALS among non-Chammorros of Guam as well as on Saipan and Tinian, and possibly in New Guinea; and 4) the present study on the Kii Peninsula.

Four cases of ALS from Kii and three cases of ALS from other parts of Japan have been autopsied. Pathologic studies revealed the process of Alzheimer's neurofibrillary change and vacuolar degeneration in autopsied speciments of the ALS cases from the Kii Peninsula. These changes were previously thought to be unique to the Guam cases.

A collaborative study of lathyrism has been undertaken in India. This is pertinent because of the clinical consequences of chronic lathyrism (lateral sclerosis) and the possible implication of the cycad nut which can cause lathyrism in cases of ALS in the Marianas.

An excessive manganese content in the soil and water in Guam is the basis for emphasis on this metal and its possible effect in ALS. A manganese study in Guam suggested a possible concentration of cases of ALS and/or Parkinson's Disease among miners.

A recent study of environmental factors in the Mitogawa area has revealed a high content of manganese in soil and drinking water located in the area of mines which are currently not in use, and chemical analysis of rocks found in these mines showed a high concentration of manganese. Systematic chemical analysis of manganese in human nervous system tissues has been carried out by means of the neutron activation method. Normal distribution of trace metals including manganese in autopsied specimens of human brain have been found.

Parkinson's Disease

A most significant finding in the last two years has been the effectiveness of orally administered L-Dopa in the treatment of Parkinson's Disease. Of the first 100 treated patients reported on by one research center, 75% were improved from 20 to 100% in their disease symptoms. The greatest

effect was on rigidity and akinesia, though tremor was reduced as well. Improvement on most patients has extended up to 13 months and longer. It is clear that L-Dopa is unmistakably superior to any other drug heretofore available for the treatment of Parkinson's Disease. However, adverse reactions have appeared which restrict its clinical usefulness such as: nausea, vomiting, postural hypotension, cardiac dysrhythmias and involuntary movements. The relatively large doses necessary to achieve and maintain clinical improvement (up to 8 grams per day) has led to research for improved analogs or the combined use of L-Dopa with a decarboxylase inhibitor in an effort to more readily secure and maintain adequate levels of dopamine in blood and brain.

The therapeutic effectiveness of L-Dopa in Parkinson's Disease has raised the question of a disorder in catecholamine metabolism as an underlying cause. L-tyrosine, the immediate precursor of Dopa, does not improve the disease symptoms when administered. Studies in the turnover rate of labelled dopamine and norepinephrine do not indicate any disturbances in the metabolism of these amines, at least in extracerebral structures.

There are two predominant biochemical abnormalities in Parkinson's Disease. One is a decrease in dopamine, norepinephrine and serotonin in the basal ganglia and two, a decrease in neuromelanin in the substantia nigra.

A constant finding in both idiopathic and postencephalitic Parkinsonism is the degeneration of nerve cells in the nigra system and diminution of melanin in these nerve cells. The presence of neuromelanin appears to be essential for normal dopamine production in the substantia nigra and in Parkinsonism the melanin granules contain less melanin as compared to normal.

Chlorpromazine commonly produced Parkinsonism-like extrapyramidal symptoms and this may be related to the interaction of this drug with melanin in the substantia nigra or with an effect on catecholamine metabolism in the basal ganglia. Experiments have indicated that chlorpromazine stimulates melanization in certain cells, probably by activating tyrosinase which has been reported to be present in the substantia nigra. Theoretically, one might expect an activation of the substantia nigra tyrosinase to shunt tyrosine from the catecholamine pathway to the production of melanin. A reduction in dopamine in the nigra body would biochemically mimic changes in Parkinson's Disease.

It was the basic research on the biogenetic amines which led to the observation that dopamine was deficient in cells of the basal ganglia and hence to the trial first of dopamine and then of L-Dopa as a therapeutic agent. Various experiments have demonstrated that dopamine can produce marked increases in motor neuronal excitability and can enhance both flexor and extensor monosynaptic reflexes.

The chemical, dimethoxyphenylethylamine (DIMPEA) is of interest because it is considered to be a normal metabolite of dopamine and because of its possible relationship to Parkinson's Disease and mental illness.

Also in this regard is Mescaline 3, 4, 5-trimethoxyphenylethylamine. Both chemicals, when given by injection, produced a series of motor disturbances similar to those produced by cholinergic stimulation in the brain. DIMPEA was slightly less potent than Mescaline. Dopamine itself was found to be inactive in this regard; as was also homovanilic acid, the final metabolite of dopamine.

Convulsive Disorders

Epilepsy is a collective term applied to abnormal brain functions which are manifested in convulsive disorders. The spasms are characterized by sudden over-activity of the brain cells resulting in loss of consciousness, thought and self-control. The severity and longevity of the seizures depend upon the kind of epilepsy and the causes from which the disease has developed.

In epilepsy, known as "grand mal" the attack is most violent. The afflicted person may bite his tongue and invariably he loses control of his faculties. The recovery period is relatively long and requires a rest period after the attack is over. In "petit mal" the seizure is of a short duration, the attacks occur more frequently, sometimes as many as a dozen a day. Seizures are characterized by jerky movements of the muscles of the arms and neck. Included in this class are infantile spasms or quivering spells. If the area or areas of the brain can be located from which these abnormal electrical discharges emanate, the affliction is termed as "Focal" or Jacksonian" epilepsy. The seizure generally starts in the extremities and/or in one corner of the mouth. The affected part trembles violently. The trembling movement moves upwards. It either ends up in a minor seizure or the individual may lose consciousness just the same way as it happens in grand mal. By far the most common type of focal seizures is the one in which the discharging neurons exert their influence upon the metal processes as well as upon the muscles. The characteristic features of this type of "psychomotor epilepsy" are: sharp and sudden pain in the stomach, dreadful fear, flinging of arms aimlessly, smacking of lips, and other incoherent physical and mental behaviors. When a person regains his normal consciousness, the experience undergone during the attack is completely lost.

Epilepsy may be caused by several factors, such as brain damage, presence of a scar caused by a wound or an injury, drugs, congenital malformation, nutritional deficiencies, metabolic abnormalities, fever (in infants), infectious diseases (encephalitis, meningitis), brain tumors and abscesses. Heredity plays a very small role in the induction of epilepsy. If one twin develops epilepsy, the other one is likely to develop it also. However, parents with this disease do not necessarily have epileptogenic offspring.

The fundamental problem is to understand the basic mechanism involved in this disorder and to develop techniques to control it. A variety of techniques have been applied to the study of nerve cell activity. One important defect in epilepsy is the uncontrolled electrical discharge from nerve cells. A device know as the electroencephalogram (EEG) has been

developed which picks up electrical signals from the brain cells, amplifies them and records the impulses in the form of graphs. Electroencephalography is the most useful tool for both diagnosis and research. With its help electrical energy discharge patterns in groups of brain cells, and in various areas of the brain, are recorded. Also with the help of microelectrodes electrical activity of a single cell can be recorded.

Functionally, each neuron builds up a supply of electricity through the action of its metabolites. By repetitive activity of charge and discharge, the cells become overactive and fire off irregularly. The firing pattern may spread to other areas of the brain resulting in an epileptic seizure. When the neurons start firing again in harmony then the seizure is over. Brain waves so monitored give no indication of the individual's intelligence, thoughts, or his mental health. However, they provide strong clues as to whether or not a person has epilepsy. An EEG recorded during a seizure is likely to show unusually high bursts of energy release. The pattern indicates the type of seizure an individual has suffered.

Experimentally, epilepsy has been induced in animals with the use of various chemicals such as antibiotics (penicillin) and by the injection of metals and/or metallic oxides. Investigations with iron hydroxide, magnesium hydroxide, zinc oxide, chromium oxide, and mixed earth oxides showed that all these oxides or hydroxides are without epileptogenic effect when applied to the motor cortex of the monkey. On the other hand nickel and antimony proved most epileptogenic only when implanted as pellets into the motor cortex. Mild effects were observed with bismuth, zirconium, tin, titanium, molybdenum and tungsten. Twenty three more metallic powders have been tested on the sensorimotor cortex of monkeys. Some have shown very severe effects, while others remained ineffective.

Monkeys with temporal epileptogenic foci began to show seizures without loss of consciousness two months after the alumina cream was injected. Monkeys with an occipital focus had no clinical seizures, but developed EEG spikes in the ipsilateral occipital cortex a month after the alumina injection. The aim of these studies is to elucidate the neural mechanism involved in the transition of a localized lesion in the brain to an epileptogenic zone. This type of experimental approach has contributed new methods of inducing chronic epilepsy in animals which provides an important new tool for the study of this disease. Applying EEG techniques to these experimentally induced epileptic animals, efficacy of new drugs is being tested, epileptic loci (foci) have been determined, and new and improved surgical techniques for therapeutic application are being developed.

Treatment of epilepsy is concerned primarily with the medical and surgical approaches. Before surgery is performed, it is necessary to ascertain that the seizures originate wholly or in part from an area of the temporal lobes that can be safely removed without causing serious neurological damage; the seizures occur frequently and are incapacitating and presently available drugs are ineffective in controlling the seizures. Also, the surgery must be accomplished so as to avoid creating a secondary scar which

may in turn cause recurrence of the seizures.

Several physio-chemical differences between normal and epileptogenic tissues have been observed. Notable of these is that the tissue from the areas giving rise to abnormal electric discharge did not bind to itself nearly as much acetylcholine as did the normal tissue. This metabolite has been shown to occur in high quantities in epileptic regions of the brain, which suggests that when this substance accumulates, seizures result.

Nerve excitability is greatly influenced by variations in the chemical constituents of the fluids both inside and between the cells. Factors that modify the balance of these constituents, such as sodium and potassium, require a great deal more investigation. A series of amino acids, such as gamma aminobutyric acid (GABA), have been shown to be involved in the excitability of nerves. In this connection, a deficiency of vitamin B6 (pyridoxine) has induced seizures by producing a deficiency of GABA. Also a number of know convulsant toxins appear to interfere with the use of GABA in the body. Disturbances of electrolyte balance may be related to the common convulsion during fever in infancy. Information about the cause and correction of such disturbances may be applied to reduce the severity of recurrent epileptic attacks and to reduce the possibility of permanent brain injury which may be caused by such episodes.

Hypothermia (90° - 92° F) as a tool in therapy of patients with acute cerebral lesions such as; cerebral contusions, cranial hemorrhage, tumors and cardiac arrest has been tried. Patients that were in status epilepticus, or had intermittent seizures which could not be controlled by medication, were completely relieved of attacks or at least were benefited by cooling. Local cooling of the epileptic brain resulted in the suppression of spiking activity which also facilitated its response to anticonvulsant drugs. From this study it was concluded that hypothermia is another treatment for problems of status epilepticus where drugs are not effective or are contra-indicated. In this treatment no complications were observed that could be attributed to the hypothermia.

The treatment of epilepsy has depended to a major extent on drugs. One of the earliest medications, was a sedative called bromide. This was followed by another sedative, phenobarbital, which worked better but caused drowsiness in some cases. About twenty years ago diphenylhydantoin (Dilantin) was introduced in the treatment of epilepsy. It has been widely used and has proved to be a valuable anticonvulsant drug. However, it was soon recognized that ataxia sometimes occured as a complication of therapy with this drug. The ataxia may develop rapidly over a period of a few days or insidiously over weeks or even months. One unexplained feature about this ataxia is the fact that occasionally a patient will rapidly develop ataxia in spite of having taken the same dose of Dilantin for several years. It has been held that ataxia is a benign symptom only requiring a reduction in dosage or occasionally withdrawing of the drug. It was, however, later conclusively shown that cats subjected to Dilantin medication had developed severe loss of Purkinje cells in the cerebellum and cystic gliosis of the cerebellar white matter. A number of cases of permanent damage to the cerebellum, apparently

due to this drug, have also been reported.

Further investigation on the epileptic patients, who had suffered Dilantin intoxication indicated a high level of CSF protein levels during the period of intoxication. All the patients improved when the drug was withdrawn, but abnormal signs occasionally persisted for several months. Inhibition of the Na, K, Mg, ATPase enzyme system by Dilantin was observed which may be an important factor in causing neuronal damage. It is suggested that Dilantin intoxification may not be such a benign complication as was previously thought, but this still does not alter the fact that Dilantin is probably the most effective single drug presently available in the management of epilepsy.

The need of potent drugs of low toxicity is still paramount, especially in psychomotor epilepsy. The use of Dilantin, phenobarbital, primidone, and mephenytoin (Mesantoin) has left a relatively large group of inadequately responding patients. Recently considerable interest has been centered on the use of benzodiazepines in the treatment of epilepsy. Diazepam (Valium) has been proved to be effective in the interruption of epileptic seizures. Similarly, chlordiazepoxide (Librium) and especially nitrozepam (Mogadon) have been shown to be useful in prophylactic treatment.

Oxapepam (Serax) which is a metabolite of diazepam is easily absorbed from the intestines and is excreted quantitatively, or nearly so, as the glucuronide. Oxazepam has been widely used as an ataraxic because of the large safety ratio and the infrequent occurrence of side effects (drowsiness, ataxia, skin rash, headache, etc.). Clinical trial made it clear that Serax is a potent drug in the treatment of psychomotor epilepsy and is of low toxicity compared to Dilantin and other anticonvulsant agents. The effect is seen not only in the reduction of seizure frequency but also in the EEGs. The fact that this compound does not interact with Dilantin metabolism, facilitates its use in combination with Dilantin.

Investigations on convulsive disorders are supported by fifty-eight research grants amounting to $2,790,000.

Infectious Diseases

Infectious diseases of the nervous system include many types of illness and an equal number of research tools are employed to attack the problems. Epidemiological studies in man or animals frequently indicate whether a disease is infectious, how it is transmitted and perhaps some idea about the causative agent.

Methods most commonly employed for recognizing the presence of viral agents in cell cultures include: observations for cytopathic effects, hemagglutination, hemadsorption; interference, fluorescence and electron microscopies. With electron microscopy and immunological techniques, efforts are made to detect infectious agents. Immunofluorescent techniques are being used in diagnosing and studying brain inflammation due to viruses. Other studies are concerned with experimental encephalitis; the epidemiology of

Eastern equine encephalitis; the effects of parasites on the nervous system; testing vaccines for protection against arboviruses; and the possible role of viruses in acute neurological syndromes in children.

Other work that is being investigated includes: the after effects of infections during pregnancy where they may result in brain damage and mental retardation: analysis of viral polioencephalomyelitis in animals; an experimental measles encephalomyelitis; the mode and spread of a variety of neurotropic agents: and increasing research on the so called "slow virus" diseases which there is reason to believe may be especially important in a variety of diseases of the nervous system.

Several years ago a viral polioencephalomyelitis was identified in pigs. The virus has now been isolated from several different organs and has been shown to be an enterovirus quite unrelated to many other known viruses. All isolates but one produced polioencephalomyelitis in germ free pigs indistinguishable from naturally occurring infections.

Recently an agent causing paralysis of the CNS in rats has been isolated and is called hemorrhagic encephalitis of rats (HER). It produces acutely lethal encephalomyelitis when injected into suckling rats, including severe hemorrhagic lesions of the brain and spinal cord.

Transmission of encephalomyelitis from humans to animals and further from animal to animal, producing symptoms typical of subacute sclerosing panencephalitis (SSPE) syndrome in the animal, has provided an important new lead in isolating and understanding the causative agent in SSPE. This disease of children and young adults is characterized clinically by progressive intellectual deterioration, myoclonic jerks, and coma. The patients become severely emaciated and die from intercurrent infections. The diagnosis established during the incipient stages often shows a personality disorder or mental retardation. At that time the EEG shows slowing and dysrhythmia. However, high amplitude, low frequency synchronous waves do not develop until the patient exhibits myoclonic jerking. Spinal fluid proteins and cell counts remain normal or increase slightly during the entire course of the disease.

It has been suggested that SSPE is caused by an infection with measles virus. Indirect support has been derived from the close match between the curves representing the presence of measles antibodies in a non-selected population as a function of age, and the cumulative plot of the age of onset of SSPE. Since immunofluorescent studies seem to have ruled out the possibility of distemper virus, little doubt is left that SSPE is associated with the measles virus and the possibility that other etiological agents must be considered has become remote though not entirely disproven.

The most obvious question is concerned with the discrepancy between the clinical and pathomorphological expression of measles encephalitis and SSPE. The former is primarily an acute condition, sometimes fatal within twenty-four hours, which develops within a few days after, but sometimes prior to the exanthema. The latter runs an exceedingly chronic, remittent course with an insidious onset after the exanthema from four to seventeen

years with an apparent incubation period of eighteen months. Admittedly, this kind of measles encephalitis has not been proved to be due to a virus infection of the brain tissue. In fact, demyelination patterns together with the post-exanthematous onset have provided powerful arguments in support of an allergic encephalitic syndrome.

On the other hand, the so called incubation type of measles encephalitis manifested before the outbreak of the exanthema has always been interpreted as indicating a direct viral aggression against the brain. This view is supported by the experimental induction of clinical measles in animals five days after subcutaneous and intranasal inoculation with brain emulsion from a patient who died with acute measles encephalitis.

This comparative account illustrates that the difference between measles encephalitis and SSPE may be more apparent than real. One report indicates an instance of measles encephalitis which showed the classical features of SSPE years later.

A somewhat different aspect of the problem is provided by the concept of slow infections and slow viruses. Slow viruses are capable of producing an eminently chronic progressive disease following an incubation period of several years. This concept has been fruitful in respect to Visna, Scrapie, and Kuru. The inclusion of SSPE in this group finds support on clinical and patho-anatomical grounds. Just why the measles virus produced an acute encephalitis syndrome in some cases and behaves as a slow virus in another needs further intensive investigation.

Myxoviruses are medium sized, ether sensitive RNA viruses, which in man have the common effect of causing respiratory disease. Although they are not regarded as "neurotropic" viruses in man, mumps is the most common virus causing central nervous system infection in rodents. In these studies occasional neurons are infected by the unadapted strain and repeated passage has yielded a strain which infects parenchymal cells of the brain causing acute encephalitis. However, mumps virus in hamsters has been shown to cause a clinically inapparent infection limited largely to ependymal cells and neurons resulting in acute encephalitis.

Hydrocephalus may be caused by infectious agents contracted prior to birth. Suckling hamsters infected by mumps virus, developed a narrowing of the aqueduct of Sylvius and subsequently hydrocephalus. The narrowing of this canal responsible for draining the ventricles of the brain is the most common cause of hydrocephalus in man.

The study was conducted with experimental models to determine the histopathological changes in the brain during acute infection, and the aqueductal narrowing and hydrocephalus induction. The signs of clinical disease developed only after the resolution of the acute infection (about fourteen days) during which the lining cells of the aqueduct had been almost destroyed. Of the suckling hamsters inoculated with mumps virus, ninety-five percent developed clinical hydrocephalus. These and other histological changes were shown to be specifically related to the mumps virus infection.

Infection of human lymphocytes with herpes simplex virus apparently does not vary with the age of the host as it does in mouse macrophages. There was no obvious difference between the number of infected adult and neonatal cells. The addition of phytohemagglutinin greatly increased the number of infected cells in both types. Intramuscular inoculation of herpes simplex virus in rabbits failed to produce CNS disease. Intrasciatic inoculation caused hind leg paralysis with an ascending myelitis. However, unlike the neural spread in mice, no evidence of viral growth could be demonstrated in the nerve. This suggests a different mechanism of neural spread in different species. In a pilot study, rabbits immunized with herpes simplex virus survived a large dose of HFEM virus. Injection of adrenalin appeared to reactivate the virus with clinical signs of encephalitis in one month. A study of fixed rabies virus in mice showed that the infection was limited mostly to neurons of the rhinencephalic structures, brain stem nuclei, dorsal root ganglia, anterior horn cells, and cerebellar Purkinje cells. After subcutaneous inoculation of the virus, it spread rapidly to the CNS via peripheral nerves without evidence of infection of the endoneural cells or any extraneural tissues. Work with the Sindbis encephalitis virus in mice demonstrated a precipitous development of resistance during the second week of like, due apparently to a limitation in the spread of infection. No nonspecific viral inhibitors could be detected. Studies on mumps virus encephalitis in hamsters showed that disease and death resulted from the infection of neurons which remained morphologically normal. It is suggested that this material may be useful in investigating the "slow" viruses which seem to act in a similar way.

In Schilder's encephaloclastic sclerosis, virus-like particles were identified by electron microscopy which are distinctly different from those observed in the case with herpes simplex encephalomyelitis, but are similar to those that occur in subacute sclerosing leukoencephalitis. The nature of these virus-like particles is being investigated.

Investigations on infectious diseases of the nervous system are supported by thirteen research grants amounting to $550,000.

Cerebrovascular Disorders

In 1969 cerebrovascular research support approximated $5,407,000. This represented 95 grants, 19 of which are clinical research center grants, the remaining 76 research grants. The latter includes cooperative studies. Although individual researchers continue to pursue investigations in specific aspects of cerebrovascular disease, the main thrust of the Institute's program is in the clinical research centers, wherein teams of investigators representing basic scientists and clinical investigators coordinate and interrelate their efforts in laboratory and patient-oriented research. The number of clinical research centers has not increased in 1969 over 1968 but this should not necessarily be construed as a lack of interest. The rapid growth which made possible the establishment of 19 centers within 3-5 years more likely predicates that we may now be supporting the major clinical and basic research teams which can constitute a research center. The difficulty of attracting new young investigators to such centers remains a serious

problem as is the difficulty of establishing new research centers in institutions which have a small core or perhaps even only 1-2 investigators interested in cerebrovascular research.

Highlights of progress as reported from several of the research centers will be reported as examples of the ongoing activities in the centers. One center now in its third year of operation is making clinical and laboratory evaluations by a multidisciplinary group, which are focused through a specially designed environment-controlled dynamic angiography laboratory in an attempt to define the alterations of aortocranial hemodynamics that result during limb exercise and changes of head/body postural relationships; and the manner in which hemodynamics may be altered by other pathophysiologic and mechanical factors. They place special emphasis on the correlation of clinical information with the results of "radioisotope arteriography", cerebral perfusion estimates by inhalation and arterial injection of 133 Zenon, analysis of pulsations detected by ultrasound, catheter contrast aortography and angiography, and direct measurements of blood flow in extracranial arteries by electromagnetic flowmeters during reconstructive surgery. They hope by their studies to provide a base for development and evaluation of diagnostic tests, analyze and evaluate the results of treatment, and establish correlations of predictive values which may aid in the identification of stroke-prone individuals in large population groups. In their studies on the development of ultrasonic techniques for the investigation of cerebrovascular disorders, routine midline echoencephalography in three positions, which includes evaluation of pulsations and of ventricular size, is performed on all patients in the study. They are able to record simultaneously the pulsations from three separate areas of brain to relate the arrival delay at each point in reference to the R-peak of the ECG. Preliminary results indicate a direct temporal correlation between pulsation arrival and significant extracranial arterial stenosis. These studies will continue.

Another study being carried out at this center is on radioisotope arteriography to obtain estimates of regional blood flow. The potential of the system, a gamma (Anger) camera, multiparameter pulse height analyzer, and computer compatible magnetic tape, is being evaluated and on the basis of 1500 studies, it seems to be a highly effective tool with particular promise in the area of mass screening of patients with asymptomatic carotid bruits. Valuable information can be obtained concerning silent carotid artery stenosis and occlusion, occlusion of major leptomeningeal arteries and arteriovenous malformations, and when combined with rectilinear brain scans is a valuable adjunct in the differential diagnosis of positive brain scans due to tumor and infarction.

Another center reports the completion this year of a 4 bed intensive care unit and a monitoring systemfor ECG, EEG, respiration, blood pressure and temperature. It also includes alarms and the opportunity for automatically started continuous tape recording of cataclysmic events portended by changes in these parameters. A master control panel is provided at the nursing station, and O_2, CO_2 and suction are available at each bedside. Study of patients in the ICU are just beginning as a result of the availability of the ICU. On the other hand, it should be noted that difficulties are already apparent inasmuch as the availability of highly skilled specialty

nursing staff "around the clock" for research patients in the study poses logistical problems, the solutions to which are presently being sought. A clinical study is being developed to evaluate urokinase therapy in selected stroke patients. A protocol is being developed as are plans to obtain the necessary urokinase. Reports of progress will be made at a later date.

In this center as in others, the Anger camera is also being used to attempt a more detailed evaluation of cerebral blood flow. An interface is being built between the Anger camera and a PC computer which is currently being programmed to plot changing brain isotope content observed following the intra-arterial injection of inert gas to calculate and contour-plot regional cerebral flood flow in ml per 100 gms per minute. This group has been able to obtain a matrix of regional brain blood volume following intravenous administration of radioactive nondiffusible indicator. They plan to normalize the data and then assess regional alterations following photic stimulation.

Another study by this center relates to the work with radioactive oxygen-15. This is carried out by having the patient inhale air tagged with oxygen-15 once, and then following the rate of formation of water by brain tissue and the rate of equilibration of the tagged water thus formed with the body pool. Earlier, inhalation experiments were done almost exclusively but intra-arterial injections of blood tagged with oxygen-15 oxyhemoglobin gives a very similar picture in terms of the formation of water and the equilibration of water with body water. In patients with either vascular occlusive disease or with brain damage there has been a difference between the two hemispheres in almost all of the cases examined so far. During the past 6 months, this group has concentrated on building a special 6-probe collimated helmet that will allow the simultaneous measurement of identical points over 3 areas in each hemisphere. This has been used several times and the group reports excellent results. They hope that a more regional assessment of oxygen utilization can be made by this technique. The use of oxygen-15 presents some difficulties because of its high gamma value (511 Kev.).

Earlier annual reports refer to the variety and complexity of research problems to which the cerebrovascular clinical research centers address themselves. These problems by no means diminish in variety or complexity. Indeed, as investigations continue it becomes apparent that the complexities increase. Problems particularly relating to terminology, acceptance of specific definition of terms are of especial importance in insuring the relevance of results from one group in the hands of another group. For this and other important reasons, the annual workshops for program directors and selected staff of the research teams in the CV research centers becomes invaluable. The third workshop was held in January 1969. The indepth review was devoted to diabetes and the concurrent discussion groups were directed toward 1) Lipid Metabolism 2) Cerebral Arterial Spasm 3) Mechanisms in the Control of Cerebral Circulation and 4) Computer Retrieval of Neurologic Data.

It is now well-established that patients with severe hypertension are less likely to have strokes if their blood pressure is treated. There is little consensus when blood pressure is only moderately elevated or when it is intermittently elevated. Some evidence suggests that acute hypertension may actually induce cerebral arteriolar constriction and increase cerebral vascular resistance, or cause rupture of microaneurysms leading to a cerebrovascular syndrome. On the other hand, there exists opposition to antihypertensive therapy on the basis that the reduction of blood pressure in the face of arteriosclerotic cerebrovascular disease may induce cerebral thrombosis. The problem of whether treatment of mild cases of hypertension will prevent strokes or increase their frequency, especially in the elderly and arteriosclerotic, has never been established. There are two primary questions to be answered 1) Does drug treatment in moderate hypertension reduce the cerebrovascular recurrence rate? 2) Does blood pressure reduction influence prognosis? These are not necessarily the same questions unless one has the most accurate information possible concerning cooperation in taking medication and concerning the change in blood pressure induced.

The magnitude of the problem is substantial and requires the collective effort of neurologists and internists to arrive at some solution. The best way to solve this important therapeutic dilemma is by a cooperative (multi-institutional) clinical trial. For the past three and a half years, the National Institute of Neurological Diseases and Stroke has provided grant support for study of the long-term effect of a fixed antihypertensive therapeutic (thiazide plus rauwolfia) program on the recurrence rate of strokes in ambulatory patients with mild hypertension. Several types of strokes are included in the study, among them transient ischemic attacks and single completed episodes. Unbiased information concerning the possible deleterious effects of blood pressure lowering is being collected also, so that the precise advantages or limitations of antihypertensive therapy may be discovered. Eleven university clinics located in various parts of the United States are participating in this cooperative study. The treatment regime is consistent with that currently used in general practice and therefore generally applicable.

Preliminary studies indicate that 1) the incidence of cerebral thrombosis as well as cerebral hemorrhage can be reduced by effective long-term antihypertensive treatment; 2) cerebral atherosclerosis is not a universal prerequisite for an ischemic cerebrovascular episode; other factors favorably influenced by lowering the blood pressure may also play a role; and 3) the effects of antihypertensive therapy on stroke recurrence in cases of less severe hypertension require further study; therefore registration of new patients continues. It is anticipated that follow-up with replacement of losses will provide sufficient numbers of patients over a five-year period to answer the question posed, "Does the reduction of blood pressure affect the recurrence rate of stroke?" The investigators participating in the cooperative study believe that clear-cut answers may in some part become apparent.

At the present time antihypertensive therapy is used regularly without conviction. At the least, this cooperative study should provide data concerning the benefit or risk of prolonged lowering blood pressure in persons with cerebrovascular disease, at all levels of age and vascular deterioration.

Trauma (Head Injury)

In 1969, 50 research grants investigating specific problems in head injury were supported representing $1,900,000. Seven grants to develop head injury centers are now attacking problems in head injury in a multidisciplinary or multifaceted approach. The support for these centers approximates $826.653.

Examples of investigations being carried out in several of the centers will be described. One group is investigating the mass spectrometer on an experimental basis in animals as a means to obtain information regarding cerebral circulation in the presence of severe trauma. Studies have progressed to the point that instrumentation now being developed will make possible the application of the technic for human use. Problems have arisen in the development of a catheter suitable for human use with the mass spectrometer which is vacuum tight so that the entire molecular flow of gas will pass through the membrane. Experiments are under way to modify the intravascular catheter, resolving the apparent difficulties so that the investigations can be pursued in human trauma studies.

Another group reports that a two bed, head trauma unit has been completed for the study of seriously injured patients. Special equipment will make possible the observation of patients for the performance of certain studies, especially those related to blood gases. The relationship of pulmonary function to cerebral function and to recovery or lack of recovery of patients with serious cranio-cerebral injuries will be determined. Other studies are those related to patients who develop hemorrhagic pneumonia. The investigators' experience indicates that, if the pneumonia is not recognized during the first 24 hours after injury, it becomes intractable and often causes death. Severe pulmonary lesions may be present during the first 24 hours after injury and yet the clinical examination may be negative. Existence of the pneumonia has been indicated by determination of pO_2 and pCO_2 but the inadvertant administration of high concentrations of O_2 may cause capillary dilation and increase the tendency to hemorrhagic pneumonia. Alternatively excessive respiratory assistance may eliminate too much CO_2 and convert hypercarbia to hypocarbia. The investigative team proposes to carry out measurements of pulmonary and cardiac function within 24 hours of injury in order to understand the changes that underlie the development of hemmorrhagic pneumonia. This will lead to better methods for monitoring such patients so that optimal administration of O_2 and other therapy may minimize hemorrhagic pneumonia and increase chances of survival. Procedures to be used will include heart catheterization studies, measurement of blood gases, and radiologic methods such as angiography and scanning techniques. Particular attention will be given to measurements of pO_2, pCO_2, cardiac output, pulmonary artery pressure, and pulmonary arteriovenous shunts.

Another interesting study this group has underway is an assessment of the microbiologic flora in patients with head injury in order to determine changes that may occur and to relate changes in flora to the occurrence of clinically recognized secondary infection. To date 21 patients have been studied extensively. Organisms not ordinarily found have been identified,

and their frequency and sources tabulated. In 5 patients, illness was caused by abnormally occurring organisms, and in 10 others, illness from such organisms was suspected. Clinical illnesses included terminal sepsis in one patient and bacterial meningitis in another. By instituting careful procedures, secondary infections were reduced. It is anticipated that, by continuing investigation of sources and causes of secondary infections in patients with head injury, evidence for the need to control secondary infections may lead to significant increases of survival in these patients.

Experimental studies on the neurochemical alterations associated with head injury are continuing, the main emphasis being directed toward, a) chemical alterations in cerebral edema, b) metabolic changes in brain in acute edema, c) plasma and CSF lactate levels following head injury. The first two studies referred to are being carried out in animals, the last one both in animals and man. Methodology has been developed, and experimental studies have been initiated.

Another center is devoting its attention to laboratory and clinical studies of head injury with particular attention to the role of vascular changes in the production of cerebral edema, direct monitoring of intracranial pressure through ventricular drainage, the role of lesions in the region of the hypothalamus in the production of edema, beneficial effects of hemodilution, the use of the hyperbaric chamber in animal studies, as well as a number of other studies.

APPENDIX A

NUMBERS OF RESEARCH GRANTS SUPPORTED
IN FY 1969 AND AMOUNTS ARRANGED BY DISORDER CATEGORY

TYPE OF DISORDER	NO.	AMOUNT	% of $
ALL DISORDERS	1,798	$ 67,775,000	100
1. NEUROLOGICAL DISORDERS			
A. Chronic Neurological Disorders of Childhood	132	3,942,000	5.8
B. Chronic Neurological Disorders of Aging	60	2,371,000	3.5
C. Cerebrovascular Disorders	95	5,407,000	8.0
D. Epilepsy and Related Paroxysmal Disorders	65	2,274,000	3.4
E. Sclerosing Disorders	78	2,797,000	4.1
F. Muscular & Neuromuscular Disorders	152	5,013,000	7.4
G. Infectious Diseases	23	586,000	0.9
H. Accident and Injury	50	1,900,000	2.8
I. Tumors of Nervous System	41	982,000	1.4
J. General	360	12,200,000	18.0
ALL NEUROLOGICAL DISORDERS	1,056	$ 37,472,000	55.3

TYPE OF DISORDER	NO.	AMOUNT	% of $
ALL DISORDERS	1,798	$ 67,775,000	100
2. SENSORY & PERCEPTUAL DISORDERS			
A. Disorders of Vision	413	15,588,000	23.0
1. Cataract	(36)	(1,209,000)	(1.8)
2. Glaucoma	(35)	(1,176,000)	(1.7)
3. Retinopathy & Neurological Mechanism of Vision	(178)	(5,980,000)	(8.8)
4. Inflammatory & Parasitic	(52)	(2,388,000)	(3.5)
5. Metabolic & Degenerative	(14)	(569,000)	(0.8)
6. Strabismus & Neuromuscular	(28)	(941,000)	(1.4)
7. Injuries & Other Disorders including Tumors	(14)	(470,000)	(0.7)
8. General	(56)	(2,855,000)	(4.2)
B. Disorders of Hearing and Equilibrium	165	6,820,000	10.1
C. Disorders of Speech & Other Higher CNS Functions	33	1,991,000	2.9
D. Disorders of Other Senses	87	2,752,000	4.1
ALL SENSORY & PERCEPTUAL DISORDERS	698	$ 27,151,000	40.1
3. MULTI-CATEGORICAL	44	$ 3,152,000	4.6

May 15, 1969

Annual Report
Training Grants and Awards Branch, NINDS
July 1, 1968 through June 30, 1969

The extramural training program of the National Institute of Neurological Diseases and Stroke, formerly NINDB, includes three types of support. All funds are awarded on a competitive basis.

1. Graduate Training Grants provide funds to institutions for the establishment, improvement and support of broad, fundamental training in disciplines related to neurological, neuromuscular, sensory or communicative disorders. The primary objective of the program is to train additional needed clinical and laboratory teachers and investigators and community health and public health personnel. In addition, Special Fellowships (Traineeships) are awarded to provide individual stipend support to clinical and laboratory scientists for advanced, highly specialized research training in preparation for careers in research and academic medicine. Traineeships are awarded also to physicians for specialized clinical training to increase their expertise in the prevention, diagnosis and management of cerebrovascular disease.

2. Through Postdoctoral Fellowships, NINDS provides support to individual clinical and laboratory scientists for research training which follows immediately on receiving the doctoral degree.

3. Career Development Awards provide a substantial period of salary support for the young investigator, either clinical or laboratory, desiring experience and further training in an environment favorable to his establishment as a fully independent investigator and teacher.

NINDS has had primary research and research training responsibility for three broad categories of diseases and disorders--those relating to the central and peripheral nervous system, the communicative system and the visual system. There are, of course, areas of overlap among the three. After FY 1969, responsibility for a large majority of the grants and awards relating to vision will pass to the newly formed NEI.

Although each area has its distinctive training philosophy and needs for trained personnel, and therefore progress will be reported for each separately, certain problems are shared by all three.

The financial support afforded through the NINDS training grant and fellowship programs has played an important, if not essential, role in making it possible to establish an effective core of young basic and clinical scientists well-prepared for research and teaching in each of these three areas of medicine. Modest, but regular, budgetary increases in the past made this development possible.

It is ironic, then, that at the very point in time when manpower available to provide training leadership gives hope for approaching the needs of the next decade across the nation for competent teachers, researchers and physicians, the increases of financial support for training to make this possible have

virtually ceased.

Although in 1969, the Institute supported 310 training programs for a total of $16,929,000 all were supported substantially below the level recommended, and available funds did not allow the renewal of four approved programs nor the initiation of 17 new approved programs. In addition to 211 special fellowships (Traineeships) supported in 1968 for a total of $2,400,000 funds were not available to pay 34.

Postdoctoral Fellowships for $985,000 were awarded to 117 individuals in 1969, but there were 10 approved for whom funds were lacking.

Research Career Development Awards in 1969 were 94 in number for a total amount of $2,258,000, but 33 candidates approved with excellent priorities could not be paid.

Communicative Disorder Research Training

The number of training grants in the field of otolaryngology and in disciplines related to speech, hearing, and communicative disorders was increased by only two in 1969. Five additional approved grants went unfunded, and all 73 grants were funded in substantially lesser amounts than had been recommended, although costs of maintaining excellence in ongoing programs mount every year. Encouraging indications have appeared this year of increasing interest in training for investigative careers in the area of speech disorders, where problems are complex and training must be interdisciplinary.

Neurological Science Research Training

The number of training grants in the broad field of the neurological sciences was increased by only one over those supported in 1968. However, there were 11 new and two renewal approved applications which could not be paid from the funds available. All ongoing programs were paid in amounts reduced drastically from those recommended as reasonable to allow for satisfactory progress.

The trend noted in 1968 toward organizing training in the neurological sciences on an interdisciplinary basis has continued in 1969, with the submission of excellent training proposals embodying fresh, new approaches to the training of investigators and teachers.

Vision

There are three more training programs in the vision field in 1969 than there were in 1968 and an additional five could have been awarded, had the funds been sufficient. In this area also, the Institute was obliged to reduce grants to ongoing programs even below levels currently being received.

There has been a recent upswing in the number of programs which can provide training in ophthalmic pathology, largely because NINDS training grant and fellowship support in the past has increased the number of scientists specially prepared for research and teaching in this important but understaffed area of

vision research. This is the last year that training grants and fellowships in the field of vision will be a part of Institute responsibility. They will be transferred on July 1, 1969, to the new National Eye Institute.

Appendix A

Distribution, by Scientific Fields, of Training Grants Supported in Fiscal Year - 1969

Fields	No.	Amounts
Neurology	73	$ 5,208,000
Ophthalmology	56	3,205,000
Otolaryngology	49	2,864,000
Cerebrovascular	6	185,000
Communicative Disorders	8	362,000
Medical Audiology	9	374,000
Neuroanatomy	6	247,000
Neurobiology	2	40,000
Neurochemistry	2	133,000
Neuropathology	14	629,000
Neuropharmacology	4	232,000
Neurophysiology	13	682,000
Neuroradiology	9	254,000
Neurosurgery	25	888,000
Neurological Basic Science	3	150,000
Ophthalmic Pathology	1	49,000
Otolaryngology & Audiology	2	212,000
Pediatric Neurology	18	727,000
Sensory Physiology - Vision	3	151,000
Sensory Physiology - Oto.	1	20,000
Speech Pathology	3	234,000
Speech Pathology & Audiology	2	75,000
Vision Psychophysiology	1	8,000
TOTAL	310	$16,929,000

May 15, 1969

Appendix 2

Distribution, by Scientific Fields,
of Special Fellowships Awarded in FY 1969

Fields	No.	Amount
Audiology & Speech Pathology	7	$ [illegible]
Biophysics	[illegible]	[illegible]
Cerebrovascular	[illegible]	[illegible]
Neuroanatomy	3	[illegible]
Neurobiology	2	[illegible]
Neurochemistry	[illegible]	[illegible]
Neuroendocrinology	2	[illegible]
Neurology	12	[illegible]
Neuropathology	21	210,[illegible]
Neuropharmacology	[illegible]	[illegible]
Neurophysiology	21	2[illegible],700
Neuroradiology	19	221,300
Neurosurgery	[illegible]	[illegible],200
Neurovirology	[illegible]	[illegible],400
Ophthalmology	3[illegible]	[illegible],000
Otolaryngology	[illegible]	[illegible],000
Pediatric Neurology	[illegible]	[illegible],000
Physiological Psychology	4	[illegible],400
Sens. Physiology - Vision	[illegible]	[illegible],000
TOTAL	211	$2,[illegible],000

May 15, 1969

Appendix C

Distribution, by Scientific Fields, of Fellowships Awarded in FY 1969

Fields	Research Career Awards		Research Career Development Awards		Postdoctoral Fellowships	
	No.	Amount	No.	Amount	No.	Amount
Audiology	1	$29,700	5	$112,700	-	----
Cerebrovascular	1	30,000	2	44,500	-	----
Neuroanatomy	2	43,100	1	17,800	6	48,000
Neurobiology	-	----	-	----	3	26,500
Neurochemistry	1	31,800	10	241,900	12	96,000
Neurocytology	-	----	4	86,500	7	61,000
Neuroendocrinology	1	26,000	-	----	4	29,700
Neurology	2	61,800	4	106,400	10	94,500
Neuropathology	-	----	6	141,300	3	24,000
Neuropharmacology	2	58,600	9	208,300	7	61,000
Neurophysiology	1	30,500	26	613,200	31	254,700
Neurosurgery	-	----	-	----	4	30,000
Neurovirology	-	----	3	65,800	2	16,900
Otolaryngology	1	32,400	-	----	1	10,000
Ophthalmic Pathology	-	----	3	67,000	3	26,000
Ophthalmology	1	32,400	5	152,300	8	70,300
Physiological Psychology	1	27,700	4	126,400	3	26,000
Sensory Physiol. - Vision	-	----	9	198,300	6	53,600
Sensory Physiol. - Oto.	-	----	3	75,600	5	40,000
Speech Pathology	-	----	-	----	2	16,800
TOTAL	14	$404,000	94	$2,258,000	117	$985,000

May 15, 1969

Annual Report
Associate Director's Report
July 1, 1968 through June 30, 1969
Extramural Programs
National Institute of Neurological Diseases and Stroke

The details of mission accomplishment of the Institute's Extramural Research and Training Program, as well as the specific problems associated therewith are included in the reports of the responsible Extramural Program Branch Chiefs. In broader administrative and scientific terms, however, the NINDS Extramural Programs for Fiscal Year 1969 have been characterized by:

A. An improvement in providing the required professional and administrative framework for the encouragement and support of research and training central to the mission of the Institute but yet responsive to the needs of the scientific community. A great deal of staff effort and time has been devoted to defining on an operating level the fine but critically important differentials between (1) mission-oriented directed research and the necessary non-directed, but mission-oriented growth of the neurological, visual, and communicative sciences and (2) providing for adequate stewardship of public funds yet avoiding administrative procedures which are burdensome to grantees and only of secondary importance to good management practices. The success of these efforts is dependent upon a continuing inter-action between the professional and administrative members of the staff and between the staff and representatives of the scientific community. This interchange has flourished during Fiscal Year 1969 and has been characterized by its constructive consequences. Reports from our advisory groups, consultants and grantees strongly support the Institute's philosophical approaches to program development and program management. A reorganization of the Research Grants Branch has helped provide a stronger base for this. In both the Research and Training Programs, the principles of organization focus upon the concepts of (1) each grant having a single manager responsible for both the professional and administrative aspects of the award, (2) each member of the staff being responsible for the development of broad disciplinary areas of research or training (e.g.: clinical neurology, basic neurosciences, human communications, etc.), and (3) specific members of the staff assigned to selected special areas of NINDS mission in accordance with scientific opportunity, program need, and staff skill (e.g.: L-DOPA, Stroke, Cerebral Death, Aphasia, Diabetic Retinopathy, etc.). This has provided a stable framework for the continuing, detailed operations of ongoing programs and the opportunity for special effort in selected areas of program responsibility.

B. A continuing increase in Extramural Program professional and administrative responsibility with an associated decrease in staff size and flexibility. The year has been characterized by additional increases in both the need for detailed professional decision making and grant negotiations and a steadily increasing number of managerial requirements originated by the Department of HEW and the NIH; concurrent with this assigned increase in responsibility and administrative procedure has been an eroding away of staff size and morale through personnel restrictions and minimally adequate personnel management practices; some examples of the latter include long delays in personnel

actions, lack of periodic reports on pending personnel requests, and the using of patterns of organization rather than the level of staff responsibility in the assessment of grade levels. The combination of decreasing staff morale and increasing responsibility poses serious threats to an operation whose administrative standards are those of excellence, and presents the danger of its conversion to one which will be satisfied with levels of performance that are minimal but adequate. Because of this alarming situation, Extramural Programs is faced with the need to develop methods by which the Institute can both discontinue specific Extramural Programs and decrease selected administrative operations of a non-legal variety.

C. A substantial deficit in required research and training funds, the latter being of such consequence that a complete reassessment and redesign of the Institute's Training Programs for Fiscal Year 1970 becomes essential. In both the Research and Training Grant Programs in Fiscal Year 1969, reductions in every grantees' budget were individually negotiated to a level at which further reduction in Fiscal Year 1970 would mitigate against the feasibility of attaining the grant's objectives. Because of this and a critical need to initiate selected new activities of high program relevance, a reassessment of Institute grant objectives and methods has been initiated. This is particularly true in the training area where factors need to be weighed such as the relative needs for additional academic and research personnel in the clinical sciences versus preclinical sciences; the relative importance of support of the training environment versus support of the trainee and the most appropriate administrative instruments of award in each area; the appropriate levels of trainee or fellowship stipend and the relative responsibilities of the training institution and NINDS in providing for these; and the point in a trainee's career when "career development" stability is most critical and productive. In addition, select committees of NINDS consultants are reviewing the national status of specialized clinical training, clinical personnel requirements for providing urgently needed patient care, and the role of the Federal establishment in providing for specialized clinical training.

D. Staff discussion and the preparation of an Institute position in regard to the over-all goals of the NINDS for the decade of the 1970's, particularly as these goals related to problems of clinical trials and to the development and evaluation of controlled community clinical demonstration and evaluation activities. In selected areas of national need, for example, trauma to the brain and spinal cord, the Extramural staff is exploring the feasibility of establishing carefully structured national centers of excellence for research, teaching and patient care as national models for community or regional action. In such national centers of excellence the differential among clinical research, teaching and patient care can be kept to an absolute minimum and a comprehensive program aimed at the total medical problem of the handling of the acute lesion of life threatening consequence and the prevention of permanent damage. It has been proposed that this "National Models Program" be launched on a pilot basis in selected problem areas such as trauma to the brain and spinal cord, epilepsy, and stroke; it would complement the NINDS active research project, clinical center and training programs in these same areas.

E. Selected areas of program responsibility have been given special attention, including (1) L-DOPA: Upon advice of an NIH panel of scientific experts, the Institute did not move forward with a prospective controlled evaluation of the efficacy and human toxicity of L-DOPA in the treatment of Parkinsonism. A retrospective analysis of available data indicated that L-DOPA probably was clinically efficacious, showed varying degrees of toxicity, and that the known adverse reactions were probably medically manageable. Two corporations in the pharmaceutical industry have launched clinical trials of the chemical in preparation for the submission of an N.D.A. to the Food and Drug Administration. The Institute is observing these trials, initiating selected studies of its own in areas not being adequately explored by the scientific community, developing 4-5 centers of research excellence for long-term studies of basal ganglia and extra pyramidal disease and its treatment through clinical center awards, and organizing workshops on specific scientific and medical aspects of biogenic amines and the nervous system; (2) stroke: having initiated 19 cerebrovascular clinical research centers through its clinical center and specialized research center programs, the Institute has now begun to select those centers in which long-term clinical research and laboratory efforts have the highest probability of success, and will discontinue the others. This "weeding out" process will take approximately two years at the conclusion of which up to ten clinical research centers will remain and serve as national focal points for research and training on problems of the cerebrovascular diseases; (3) human communication: a three-year effort has been completed in which the total national problem of human communication and its disorders has been assessed and a comprehensive report prepared describing the state of this national problem, the present efforts being taken to meet these needs, and plans for meeting them; appropriate parts of the report will be published and distributed. Using this report as a working document, the Institute will evaluate its own efforts in this program area and initiate selected additional activities as staff, funds, and opportunity permit; (4) visual disorders: retrolental fibroplasia, a previously major cause of blindness in the USA, has begun to reappear as a result of oxygen therapy of the acute respiratory distress snydromes of the premature. The Institute has initiated a cooperative study to develop methods by which blood oxygen tensions can be measured more precisely in clinical situations and more exacting standards of oxygen therapy established which will provide for metabolic needs but still be below dangerous levels of visual development. Also, because of the unsatisfactory status of therapy for diabetic retinopathy, the NINDS has inaugurated a cooperative study to evaluate the efficacy of presently available methods of therapy.

F. Staff reorganization and operational modernization. A formal reorganization of the professional and managerial staff of the Extramural Programs has been completed in order to provide for greater identification and authority where responsibility for program operation exists. As part of this, the Research Grants Branch has been sectionized and within each Section staff scientists designated in the areas of the basic neurological sciences, the clinical neurological sciences and the communicative sciences; the same designations occur in the training areas. Despite this reorganization, the principle of a single staff scientist having total responsibility for all professional and managerial decisions on any particular grant has been maintained. Also, the

operations of the data reports and analysis section, OAD, have been reorganized to provide for conversion of a marginal punch card data storage and retrieval system to one utilizing the computer facilities of both the DCRT and DRG. This will provide for greater efficiency of operation but at the cost of less flexibility in data management; these latter compromises are the result of restrictions on the recruitment of necessary technical and clerical staff.

G. The initiation of the activities of the National Eye Institute. A National Advisory Eye Council has been appointed, an orientation and planning meeting held in March 1969 and a regular meeting held in June 1969. In addition, with the assistance and cooperation of the DRG, the philosophical and operational dissection of the grant and award programs of the NINDB into the NINDS and NEI has been completed. During Fiscal Year 1969, the Extramural Program staff of the NINDS continued to carry all responsibilities for NEI grant and award programs. Because of the continuing attrition of personnel, however, the over-all percentage of NINDS staff time available for this has decreased and continues to grow less. In Fiscal Year 1970, the staff of NINDS plans to assist the newly designated staff of the NEI in a supportive role, instead of as the responsible agents of the new Institute. The techniques and guidelines for this have been developed and are now operational.

Annual Report
July 1, 1968 through June 30, 1969
Research Grants Branch
National Institute of Neurological Diseases and Stroke

Introduction

The name of the Institute has been changed twice during the past year. With the legal authorization for the establishment of a National Eye Institute on August 16, 1968 the name was changed to National Institute for Neurological Diseases. It was later changed to National Institute of Neurological Diseases and Stroke. However, these changes have not affected the mission or activities of the Research Grants Branch in that the research grant programs of the NEI have continued to be the responsibility of the Branch during FY 69.

The scientific approaches to, and the scientific advances made in the various disorder categories within the mission of NINDS are summarized in subsequent sections of this Report. Therefore, comments here are limited to a few generalizations pertaining to both scientific and administrative aspects.

About a year ago data became available from several investigators, most of whom were supported by NINDS, to indicate that L-Dopa (3, 4-dihydroxyphenylalanine) might be highly effective in the treatment of Parkinson's Disease. These preliminary data indicated that at least 50% of the patients showed remarkable improvement and another 25% showed appreciable improvement. Even though the doses were large and serious toxicity would occasionally develop, the therapeutic potential of L-Dopa was considered very important. A proposed cooperative study of 20 institutions to evaluate this therapy was disapproved by expert consultants with the hope that data already available might answer the major clinical questions of efficacy and toxicity. This turned out not to be the case. Further review of the situation indicated that studies already supported by commercial pharmaceutical firms to satisfy FDA requirements plus projects presently supported by NINDS and other agencies would soon provide needed clinical data without further support from NINDS. Perhaps the most important needs for the future are 1) the synthesis and testing of one or more analogues or potentials of L-Dopa which will be more effective with less toxicity and 2) the additional insight into the chemistry and metabolism of the brain.

Research supported by this Institute virtually eliminated retrolental fibroplasia by the discovery in the early 1950's that it was usually caused by the exposure of infants to high oxygen concentrations. The more recent use of oxygen for hyaline membrane disease and other respiratory distress syndromes in infants has reopened the whole problem. Investigators at five institutions have just begun a two year cooperative study to establish safe guidelines for oxygen therapy in the premature infant.

There is considerable concern about the increasing incidence of diabetic retinopathy and the lack of a really satisfactory treatment. The NANDS Council has recommended support for a Planning Committee on Diabetic Retinopathy to 1) review the literature 2) identify research needs in the natural history and therapy of the disease and 3) develop an experimental animal analogue. Support has also been provided for a series of three workshops over five years to explore the development of studies on specific aspects of diabetic retinopathy.

After several years of work, the NANDS ad hoc Subcommittee on Human Communications and Its Disorders has submitted a three-volume report with twenty-six specific recommendations. The report includes a detailed analysis of the present state of research and training in this area. The recommendations are presently under review by the Council. Their implementation would increase research and research training in Human Communications by about 100% during the next five years.

The NANDS ad hoc Subcommittee on Rehabilitation also has submitted an extensive report on problems of blindness rehabilitation; this report is under review by the newly established National Advisory Eye Council. The work is concerned with the concentrated application of systems analysis and conceptual models to the study of blindness and services to the blind in the United States.

A new administrative problem this year was the negotiated reduction of every research grant, competing or committed, in order to have funds to award a reasonable number of new and renewal grants. All grants were individually negotiated downward by an amount which would still allow the work to proceed, although productivity was unquestionably reduced.

The Research Grants Branch was fortunate in maintaining a stable and experienced staff during the year. The transfer to the National Eye Institute of work on vision and its disorders will result in the loss of one professional staff member and will lead to an increased work load for all other members of the staff, because the one staff member has been responsible also for several areas other than vision. Because of increased activity in the Special Programs, some research project responsibilities from that area will have to be reassigned. These changes will require that the staff member lost because of the transfer to the NEI be replaced as soon as possible.

This year 1,798 research grants were supported at a total cost of $67.8 million. Last year the comparable figures were 1,780 grants for $65.1 million. The numbers of grants and amounts of funds in the various disorder categories are shown in Appendix A.

COMMUNICATIVE DISORDERS

Progress in research in the communicative sciences supported by the National Institute of Neurological Diseases and Stroke has been highlighted by many valuable contributions to the general understanding of the underlying mechanisms and dynamics of normal human communication and the several diseases which impair it.

Sensory Processes

In the area of sensory processes one investigator reported three major accomplishments. Work progressed on 1) the determination of a general decay time constant in the peripheral and low central auditory system 2) determination of the acoustic impedance at the human eardrum up to a sound frequency of 7000 Hz and 3) determination of subjective vibrotactile intensity as a function of vibration amplitude and frequency. Investigations of central auditory masking and comparison of their results with neurophysiological recordings have shown that single neurons as well as groups of neurons of the 8th nerve, the cochlear nucleus, and the superior olivary complex fire at a rate which is maximum near the onset of stimulation and decays exponentially with a time constant of about 50 milliseconds. The decay time constant, as derived from central masking and neural recordings, appears independent of stimulus and of the tonotopic location. The invariance of the time constant with the neural level and its direct reflection in a behavioral response strengthens the evidence for the linearity of the central auditory system.

Inner Ear

The ears of seven chinchillas with complete section of the tract were examined by electron microscopy, along with normal animals. Results show that the outer hair cells are supplied for the most part (although not completely), by the crossed efferents, whereas the homolateral efferents are restricted to the inner spiral and tunnel bundles. Input-output function for cochlear microphonics as well as whole nerve action potentials, were measured at 1000 Hz in the ears of three animals at 14, 17, and 96 days after tract section. Responses were also measured in three animals just before and after tract section. Some differences in response before and after tract section were present, but these were no greater than variations encountered among normal ears. An endolymphatic hydrops experiment involving a light microscopic study of guinea pig inner ears operated upon for blockage of the endolymphatic duct and sac has been completed. The essential findings were the presence of hydrops in all sixty-one operated animals and frequent demonstration of lesions in the sensory cells, spiral ganglia and stria vascularis at the apical turn of the cochlea; the vestibular neurosensory elements remained essentially unchanged. None of the control animals showed hydrops.

Hearing

Electrophysiological experiments on cats with several electrodes permanently implanted within the cochlea suggest that it is becoming reasonably certain that some types of deafness related to cochlear defects are at least within the realm of surgical therapy. Twenty-four chinchillas have been exposed to a series of moderate intensity noise. Results indicate that although group means were stable from week to week when the same noise exposure was used, individual values of temporary threshold shifts (TTS) varied greatly. The noise was increased to 124 dB SPL. A two-hour exposure at this intensity produced permanent threshold shift (PTS). Analysis revealed none of the tests of TTS, the presumed predicator of PTS, showed significant correlations with the final PTS. In another series of studies on loudness, one researcher reported that the Physical Correlate Theory applied to loudness judgements considers that twice subjective levels of self-generated (autophonic) sounds are equivalent to estimates of the increase in sound level required to project ones voice twice distance. The Physical Correlate Theory considers that subjective magnitude judgements of both distance senses, vision and hearing, are based upon experience with changes in distance. In utilizing a new technique involving intracellular recording on the isolated spinal cord of the frog, an investigator was able to determine whether in the central nervous system there occurred a natural spontaneous release of transmitter from the presynaptic terminals. There had been conflicting evidence concerning the origin of so called "synaptic noise". The investigator showed that after all elicited impulses were blocked by tetrodotoxin, miniature synaptic potentials could still be recorded at rates not significantly different from those before the administration of the drug. These results suggest that in the isolated spinal cord of the frog, the miniature synaptic potentials were analogous to miniature end-plate potentials at the neuromuscular junction.

Hearing Disorders

Work is proceeding in establishing norms for the various parameters of human stapedial and tensor tympani reflex actions in normal populations and to compare results in patients with various middle ear pathologies. The method employed uses both impedance audiometry and typano-manometry. Electrodermal audiometry has aided in resolving the controversial question concerning hearing impairment associated with Rh incompatibility. Results of this study strongly indicate lesions low in the central auditory nervous system (cochlear nuclei) or in the peripheral sensory-neural mechanism (cochlea), not at high levels in the central auditory system. This localization of damage is an important step in understanding the nature of the impairment and in facilitating more effective aid to the individual. Significant damage to the organ of Corti was found to occur when chloramphenicol was experimentally appled to the middle ear in a large number of guinea pigs. The study was conducted to histologically evaluate and localize damage resulting from the direct application of chloramphenicol to the window of the middle ear. Wide spectrum chloramphenicol has been widely used by otologists because of its effectiveness when applied topically

to the middle ear in cases of chronic refactory otitis media and following typanomastoid operations. The histologic results indicated that chloramphenicol used in this way produced hearing loss through extensive damage to the organ of Corti and variable damage to the stria vascularis in the basilar turn of the cochlea. These findings should alert otologists to the danger of using chloramphenicol topically in the middle ear.

Bone Banks

In one Temporal Bone Pathology Laboratory, a total of 67 pairs of human temporal bones were received within the first six months. In almost every instance the brain was collected simultaneously. These brains are prepared for histologic study in the Neuro-pathology Laboratory. The anatomical material collected from these various sources represent a broad variety of valuable pathology which in every instance involves cochlear and vestibular system or other structures of the temporal bone.

Comparative Hearing

Further work is continuing on the structure and function of the ears of lower vertebrates especially the lizard. The results will extend our understanding of the relations between the details of structure and performance of these ears as shown by cochlear potentials. These results will also provide a better estimation of the degree to which different lizard species have developed pitch discrimination in terms of place representation along the basilar membrane. In an investigation of the function of the round window in the frog, evidence has been obtained by blocking this window that it serves as a yielding point in the action of sound pressures on the inner ear, just as it does in the higher vertebrates. Substantial progress has been made in studies of the use of echolocation by bats in the location and identification of objects. This manner of object perception is being analyzed in an effort to determine the particular acoustic cues utilized by the bat in different situations. It has been found and verified that the bat used temporal information in the discrimination of distances.

Hearing and Heredity

In experimental studies in hereditary deafness, 125 patients in 35 families have thus far been examined in a hereditary deafness clinic. Three families with dominantly inherited low frequency hearing loss have been identified and special audiologic testing has permitted a clear delineation of this newly recognized genetic entity. In addition, several patients with unusual chromosome anomalies have been examined, resulting in a definite description of laryngeal abnormalities in the Cri-du-Chat syndrome. A new syndrome of cochlear deafness, high myopia, and intellectual impairment is presented. Four of seven siblings are affected in an inbred Amish family, indicating a simple autosomal recessive mode of inheritance. None of the mentally unaffected siblings are myopic or have hearing problems.

Speech

In otolaryngology and speech pathology one researcher pointed out that to understand and provide rational therapy for phonatory voice disorders, it is necessary to understand the behavior of the larynx during the production of both normal and abnormal vocal sound. Analysis of ultra high speed motion pictures of larynges supports the hypothesis that there are at least four types of normal laryngeal behavior employed in speaking: 1) open larynx, no vibration 2) closed larynx, no vibration 3) incomplete closure during phonation and 4) complete glottal closure during vibration. Analysis also reveals that the vocal cords are capable of independent vibration and are influenced by unilateral disease or other conditions. Differences in vibrational pattern between the two vocal cords causes rougher sounding voice when the composite vibration creates random irregular variations in the sound wave. In a study of aphasia, speech patterns were found to correlate with anatomical lesions. The study suggests the presence of two distinct types of aphasia occuring with sufficient frequency to warrant consideration as syndromes. Actually, it was shown that a large percentage of aphasics can be placed in one of the two groups on the basis of speech characteristics alone and that the causative lesions producing these distinctive groups arise from separate anatomic localizations. The anterior area appears capable of producing cliche type, over-learned speech patterns while the posterior area is necessary for the specific exact use of language. In 100 patients with aphasic syndrome, a lesion located anterior to the Fissure of Rolando (the speech area of the frontal lobe) was associated with low verbal output, dysprosody, dyscertheria, considerable effort and predominant use of substantive words; whereas posterior lesions (the speech areas of the parietal and temporal cortex) showed little effect on these features but resulted in paraphasia, press of speech, and lack of substantive words.

Antiviral Substances in the Cornea

Since the discovery of the first therapeutically active antiviral compound, IDU, its potency in treating experimental herpes simplex has been well documented by many researchers, and the effectiveness of the drug in man has been established in five double blind studies. The Food and Drug Administration has accepted it and it is now widely used clinically. The ability of corticosteroids to suppress herpetic stromal edema has been established and IDU can inhibit the deleterious effects of corticosteroids on epithelial disease.

The shortcomings of the drug have also become apparent. Its effective therapeutic concentration is limited by poor solubility, and the use of special non-aqueous solvents such as DMSO are of little help in increasing therapeutic efficacy. In addition to limited concentration, resistance (in tissue culture) develops rapidly. Although the drug can be given parenterally and has apparently saved the lives of several children with herpes simplex encephalitis, it is a poor drug for systemic administration. It is hydrolyzed rapidly and may alter the chromosomal patterns so that its use in only potentially fatal diseases seems justified.

In order to find better drugs, the correlation has been studied between tissue culture activity and *in vivo* activity against corneal disease. A precise double blind evaluation system for *in vivo* measurement of activity utilizing herpetic corneal ulcers has been developed. This allows one to relate the improvement in corneal disease due to treatment to the concentration of the compound in eye drops and to plot precise, reproducible dose-response curves. For the first time this allows a quantitative evaluation of the potency of topical anti-viral compounds (a type of ED_{50}), the determination of meaningful therapeutic-toxic ratios, and the precise comparison of drugs in terms of attainable antiviral activity. The tools to permit a precise evaluation of antiviral drugs *in vivo*, and this system with IDU as the positive control, is now a standard system used by most drug companies studying antiviral drugs. It has also permitted an *in vivo* study of metabolic rate-limiting steps for antivirals, which is important because these compounds can act at multiple sites. Additive or synergistic antiviral effects can be quantitated as well as competitive and non-competitive reversal of antiviral activity.

With these methods a wide variety of newer anti-metabolites have been discovered. Some, such as cytosine arabinoside, were too toxic to be useful. Others, such as methylamino deoxyuridine, (MADU) lacked potency, but one, 5-trifluoromethyl-2-deoxyuridine (trifluorothymidine or F_3 TdR), was exceedingly potent, with almost no toxicity, and almost no propensity to stimulate resistance to the drug by the virus. In rabbits, it made herpetic ulcers heal rapidly and reliably and the drug was a superior antagonist of the tendency of steroids to make herpes worse.

Glaucoma

Currently the importance of aqueous humor dynamics is undergoing analysis. If the true facility is defined as the increase in outflow of the fluid from the eye with an increase in the intraocular pressure, then pseudofacility is defined as the decrease in the flow of liquid into the eye with an increase in the intraocular pressure. Pseudofacility is affected by the hydrostatic pressure and the colloidal osmotic pressure of the blood within the vessels of the eye, the intraocular pressure and the permeability of the vascular bed. The magnitude of pseudofacility could represent one of the regulatory factors in the maintenance of intraocular pressure. Secondly, total facility (true facility plus pseudofacility) is the value measured by tonography. Subtracting the value of pseudofacility from total facility, yields true facility (outflow via Schlemm's canal). The first determination of pseudofacility in the eye of man has recently been reported. Pseudofacility was 20% of the total facility or 0.06 ul/min/mmHg.

Visual Electrophysiology

Recent investigations indicate that the Electrically Evoked Response (EER), a technique for recording the occipital response to electrical stimulation of the globe of the eye, represents a new type of measurement promising potentially useful information on visual function. It is one of several types of stimuli other than visible light used by investigators to create the sensation of light.

Both EER and the Visually Evoked Response (VER) have been useful in studying the eye. Results of the present investigations show that the EER is a distinct and separate entity from VER, utilizing part of the same pathways as the VER but differing in several notable respects. There is measurably shorter latency of the EER than the VER of the same subjective brightness, which suggests that at least one step in the retinal transmission chain has been bypassed--the rod outer segment step, or possibly the whole receptor--with the bipolar or ganglion cells stimulated. Differences in amplitudes of EER and VER of the same subjective brightness were found. The non-selective electrical stimulus appears to activate in a nonspecific way many cell trains (collateral circuits) which do not contribute to the sensation of brightness. These noncontributory circuits seem to terminate their activity in the occipital region.

In EER, the investigators sum the responses to repeated stimuli on a small special computer which permits recordings from the scalp of the intact human being. The stimuli are induced through a low vacuum contact electrode (the active electrode) and a U-shaped silver foil electrode (the inactive electrode) applied to the periorbital skin. Although there is considerable variation of EER from individual to individual, the response for any one subject appears to be constant.

The investigators report that these preliminary investigations are being expanded to include more standardization studies and investigations of disease involving retinal disorders. Expansion of investigations into EER production by other scientists seems imminent.

Rehabilitation In Eye Disorders

The special problems of prescribing suitable aids for partially sighted children have been under investigation for several years. Findings show clearly that in children with a static level of visual impairment the lens needs re-evaluating at intervals to determine when an increase in power of the reading aid is required. The two principal reasons for the changing requirements are (a) decrease in ability to sustain accommodation for a close reading distance and (b) decrease in the size of the text the child wishes to read.

Retrolental Fibroplasia

Recently high oxygen therapy has been found necessary to save the lives of premature infants who develop respiratory distress. Approximately 40,000 infants need such treatment every year. Nearly 20 years ago work supported by this Institute showed that the excessive use of oxygen therapy in such infants was the principal cause of retrolental fibroplasia which almost invariably results in blindness. Subsequently it was shown that the disorder could be prevented in many cases by constant control of the oxygen concentration in the eyes of infants while under oxygen therapy.

Despite this information there seems to have been a marked increase in the incidence of retrolental fibroplasia since the use of oxygen therapy became justified in the past few years. Many hospitals do not have facilities to monitor arterial oxygen and the levels that are safe for the retina of the premature infant are still unknown. To attack this problem the Institute has just begun to support a cooperative study including investigators at five separate institutions with the objective of establishing safe guidelines for oxygen therapy to the premature infant. The study is designed to (1) develop an improved arterial oxygen tension monitoring device; (2) determine oxygen time-dose relationships to retinal changes; and (3) examine histologically any eyes that may become available at death after exposure to oxygen. It is expected that this study will make important progress in this difficult area in two years.

NEUROLOGICAL DISORDERS

Neuromuscular Disorders

Myasthenia gravis and the various muscular dystrophies constitute the most prevalent neuromuscular diseases. The dystrophies encompass a large variety of clinical conditions and new dystrophic varients in both humans and animals are described each year. They are usually genetic in origin although dystrophic changes are observed in experimental animals subjected to nutritional deficiencies. On the other hand myasthenia gravis has been recognized as a clinical entity for several hundred years.

The symptoms of myasthenia gravis are related to impaired transmission through the myoneural junction although it has not been established whether the deficiency is prejunctional or postjunctional. In the latter case, it would signify a decreased sensitivity to the transmitter, acetylcholine. If the defect were prejunctional, it would suppose that acetylcholine synthesis or release in response to motor nerve stimulation is impaired. Current therapy is centered around the administration of anticholinesterase agents which decrease the rate of inactivation of acetylcholine at the postjunctional site. While this implies refractoriness of the postjunctional receptors, recent studies of miniature endplate potentials suggest that the sensitivity of the endplate to acetylcholine is unaffected in myasthenia. Identification of the primary cause of the disease may eventually be clarified by the use of guanidine, a drug which facilitates the release of acetylcholine from motor nerve terminals. If the defect resides in acetylcholine release, guanidine should be of dramatic benefit. If the defect is in acetylcholine formation, initial improvement should be followed by deterioration of transmission as stores are depleted. Results thus far indicate that guanidine may be of benefit to some patients while others are adversely affected. Tentatively, some investigators now conclude that the disease probably does not arise from impaired release of the neurohumor. However, the nature of the physiological defect may vary from one patient to another or with the severity of the disease.

Recent research has suggested that myasthenia gravis may be an autoimmune disease. Lymphoid hyperplasia of the thymus occurs in approximately two-thirds of all patients and occasionally thymectomy induces remission. The immunoglobulin fraction of the serum of some patients binds with the cross striations of skeletal muscle. Serum globulins from patients may also react with the nuclei of various cells, cytoplasm of the epithelial cells of the thymus, and ribonucleoprotein of skeletal muscle. The striations of skeletal muscle obtained by biopsy contained globulin in some patients, and globulin was found in the skeletal muscles of rats following intraarterial injection of the serum of myasthenic patients. According to this theory of the etiology of myasthenia gravis, the neuromuscular junction of patients is believed to be sensitive to a circulating neuromuscular blocking agent. However, efforts to directly test this idea by the administration of myasthenic serum into rats has led to conflicting results.

The muscular dystrophies have been variously associated with morphological, chemical or physiological changes in muscle, nerve, the circulation or the myoneural junction. A variety of animal dystrophies are available for experimental laboratory use. The various clinical entities observed in humans are classified mainly by histological and histochemical analysis of biopsy material. Much research in this area is concerned with the correlation of histology with electrophysiology of nerve and muscle, chemical analysis for the activities of various enzymes and alterations observed with the electron microscope.

Recently studies of the chemistry and structure of human actin and myosin have begun. Since these are the predominant proteins of muscle, detailed information of this nature may eventually prove of value in tracing the etiologies of various dystrophies via the pathways of protein synthesis.

A careful and detailed protocol for the evaluation of therapy in muscular dystrophy has been developed and is currently employed in two centers to assess the possible therapeutic effects of hexahydrocoenzyme Q4 on the course of dystrophy of the Duchenne type. This material was found to be effective in the treatment of the genetic muscular dystrophy of the Bar Harbor strain 129 mouse. The substance is a derivative of coenzyme Q_{10}, reported useful in the treatment of Vitamin E deficiency myopathy in rabbits and hamsters.

Potentially important observation of the effects of a high oxygen environment on the early course of genetic muscular dystrophy in chickens has been reported. Exposure to a 70 percent oxygen environment allowed enzyme development in the microvasculature and breast muscle to procede at a higher rate in affected chicks for the first weeks after hatching. However, the effect was absent after eight weeks of continuous exposure to high oxygen. At all times a direct correlation was observed between enzyme activity of the blood vessels and morphology of the muscle fibers.

Neoplastic Disease

A variety of procedures are employed for the diagnosis of brain tumors reflecting the absence of a standardized, reliable methodology for this purpose. This results from the heterogeneity of brain tumors in terms of size, morphology, vascularity, and metabolic characteristics. The technique used is usually dependent on the training and experience of the clinician. Careful examination of the electroencephalogram taken together with the presenting neurological signs are often sufficient to both diagnose and localize certain tumors. Angiography, x-ray visualization of radiopaque substances injected into the major arteries traveling to the brain, is currently utilized extensively. Its efficacy is based on the rate and extent of filling of the cerebral vasculature and the appearance of abnormal blood vessels. The procedure is not without risk, since the materials injected are potentially neurotoxic if not quickly flushed out of the cranial vessels, or if used in high concentrations. Current research is oriented toward reducing the toxicity of these radiopaque materials by chemical modification of the molecule and by using diluents which retard movement of material out of the blood vessel into the parenchyma.

Tumors which selectively accumulate radioactive tracers may be localized by external scanning. In this instance, it must be assumed that the blood-brain barrier in the affected area has been modified to differentially allow influx of labeled molecules. However, a growing tumor often produced edematous tissue changes in the surrounding parenchyma, including modification of the blood-brain barrier. In these instances radiotracers may enter the brain and delineate the periphery of the malignancy. Human serum albumin iodinated with I^{131} or I^{125} which is maintained in the blood relatively long periods may be utilized for localization purposes under these two circumstances where blood-brain barrier modifications have been produced.

The metabolic characteristics of certain tumors may be utilized for diagnosis. Neuroblastomas synthesize catecholamines at a high rate and this is reflected in the urine by the presence of relatively large amounts of catecholamine metabolites. A potentially important method of diagnosis currently undergoing development is based on the observation that brain tumors synthesize cholesterol actively. When cholesterol synthesis is blocked by the administration of triparanol, a metabolic intermediate, desmosterol, appears in the cerebrospinal fluid. Using clinically standardized procedures for the administration of triparanol and the sampling of cerebrospinal fluid, the increment of desmosterol observed identified 80% of tumors and no "false positives" are found. It should be noted that this method may be used to follow the course of tumor regression following therapy and to check for regrowth or the presence of metastases.

Brain tumors are usually treated by surgery and/or radiation. Often these procedures are palliative in nature since vital brain centers necessary for life may be involved and cannot be extirpated or further damaged. However, progress has been made in increasing the effectiveness of clinical techniques. Recent observations indicate that concomitant treatment with radiation and adrenocortical steroids increases comfort and prolongs life. Tumor regression has also been accomplished by surgical implantation of small radon pellets. Chemotherapy is not extensively used since agents effective in other organs generally cannot pass the blood-brain barrier. In certain instances the barrier is modified either within or around the neoplasm so that it may eventually be possible to administer effective compounds through the cerebral blood supply provided that systemic toxicity is minimized by dilution or isolation of the circulation. Cytotoxic agents placed directly in the cerebrospinal fluid have been effective in controlling meningeal leukemia, but solid tumors have not yielded to this approach as yet.

The incidence of tumors of the nervous system has recently been reported for the entire population of Israel for the years 1961 through 1965. The overall figure of 12.8 per 100,000 is similar to that observed in Sweden and the United States. However, for immigrants of European origin the incidence was 15.6 in contrast to 7.3 for immigrants from Africa. Gliomas accounted for approximately one-third of all histologically verified tumors and meningiomas for about one-fourth. The five year survival rates were 63% for the latter and only 21% for gliomas.

The cause of tumor formation is not known although evidence for a viral origin has been accumulating in the case of experimental animals. It is therefore of extreme interest that a cell free preparation of an experimental animal glioma has recently been shown to be capable of inducing tumor formation in hamsters. Furthermore, virus particles were identified in the precancerous tissue. It is obviously necessary to demonstrate unequivocally that the particles seen were actually viral in nature and that they were causally related to tumor development.

Multiple Sclerosis

A nationwide cooperative study beginning in April 1965 and involving ten University-based treatment centers has treated 197 hospitalized multiple sclerosis patients in acute exacerbation with ACTH and placebo by a double-blind technique under a strict protocol. Five methods of examination and evaluation were carried out before and at weekly intervals for a total of five weeks. Data on the multiple variables of each method were collected and analyzed by computer. A summary of the results shows that with appropriate randomization of patients and treatment, a therapeutic agent can be reliably evaluated in this disease. Careful analysis of data confirms the clinical impression that ACTH has a weak therapeutic effect, somewhat superior to placebo, detectable at the second and third weeks, but which is less definite at the fourth week following the beginning of treatment. Six to eight month follow up observations are not sufficient to provide significant information to determine the late effects.

Experimental Allergic Encephalomyelitis

The demyelinating effect of sera obtained from animals with experimental allergic encephalomyelitis (EAE) has previously been demonstrated in tissue culture. The use of this in vitro model system has been extended to a study of both lymphoid cells and serum samples from inoculated animals. Lymphoid cells were obtained from Lewis strain rats inoculated with either whole bovine white matter in complete Freund's adjuvant or with adjuvant alone. The lymphocytes thus obtained were included in the culture's nutrient medium. Simultaneously, the serum from the same animal was also included in the sister cultures; all cultures were then observed for possible demyelination. The following observations have been made: 1) both lymphoid cells and serum from an EAE inoculated animal produce demyelination in cultured cerebellum and spinal cord. Neither induced demyelination in cultured dorsal root ganglion from peripheral nerve 2) the reaction to cells and serum differ. The demyelinating reaction to serum is rapid, frequently beginning and completing its course within hours whereas the same pattern of change requires days to be completed after exposure to cells 3) preliminary experiments show that washed lymphoid cells maintained in an isolated culture, i.e., in the absence of nerve tissue, release demyelinating substances (antibodies) into their nutrient medium which then cannot produce demyelination in cultured nerve tissue.

Findings which help to explain why myelination takes place in some situations and fails in others and why synaptic connections are re-established on occasion have resulted from an extensive study of the development and myelination in culture of immature cerebellar tissue of the new born mouse. The evidence presented indicates an in vitro persistence of basic affinities between neuronal types. The results also suggest that juxtaposition may enhance myelinogenesis by increasing the number of potential contacts between Purkinje and other neurons.

The cerebellum from the new born mouse was used for study because it is extremely immature at birth and remains myelinated in vitro and in vivo for the first five to six post-natal days.

Cerebellar explants were placed either widely separated or in contiguous pairs. A striking difference in pattern of myelinogenesis and organization was apparent between single and contiguous explants. At 14 days only 14% of single explants were heavily myelinated as compared with 55% of those paired at random, and 86% of those in topographic continuity. It appears that the selective affinities between certain cells of the cerebellar cortex with which they might normally interact in vivo may influence and direct axonal regeneration leading to the re-establishment of synaptic relationships between contiguous explants.

A transient little known type of mononuclear white cell in the peripheral blood has been shown to synthesize a factor capable of breaking down myelin in experimental allergic encephalomyelitis (EAE). It has been postulated that this might also be involved in human demyelinating disorders such as multiple sclerosis. These sensitized cells (immunocytes) reproduced rapidly and demyelination was observed in cultures to begin within a few days after immunization, well before lesions appear in the central nervous system. This has broad implications in studying events preceeding demyelination in a wide range of autoimmune diseases. Utilizing cultures of these circulating immunocytes should allow intensive study of short term in vitro protein synthesis, circumventing the problem of binding action to target organs.

A rapidly increased percentage of monocytes undergoing DNA synthesis was revealed during the inductive phase of EAE by a morphologic study of peripheral blood smears. It was found that these cells usually occur in maxium numbers several days before the onset of CNS symptoms, and were virtually absent by the first clinical evidence of neurologic disease. Many of these cells were found to have an unusually high rate of metabolic activity, releasing substantial amounts of radio-active protein into the supernatent obtained by centrifuging the immunocytes. The presence of the immunocytes may be a signal of immune response of diagnostic value.

Amyotrophic Lateral Sclerosis

An endemic focus of amyotrophic lateral sclerosis (ALS) in the Kii Peninsula in Japan has been under investigation for some time. Included are epidemiologic, genetic, clinical, pathologic, histochemical and trace metal studies.

In the Mitogawa area of the Kii Peninsula a high frequency of motor-neuron disease has now been documented from fatality statistics and epidemiologic survey. Prevalence of ALS (a spinal muscular atrophy) is about one per thousand population, and of primary lateral sclerosis about two per thousand--both far in excess of that found in western countries or in other parts of Japan.

Mortality statistics reveal that ALS was responsible for 31 deaths out of 1,414 deaths in Kii area for the past 20 years. This is 10 times the average of the whole of Japan.

Though originally considered genetic, the Marianas form of ALS is now thought to be an exogenous disorder because of 1) discovery of the Parkinsonism dementia complex in these islands; 2) clinical and especially pathologic factors of both ALS and Parkinson's Disease in at least some instances of either entity 3) high frequency of ALS among non-Chammorros of Guam as well as on Saipan and Tinian, and possibly in New Guinea; and 4) the present study on the Kii Peninsula.

Four cases of ALS from Kii and three cases of ALS from other parts of Japan have been autopsied. Pathologic studies revealed the process of Alzheimer's neurofibrillary change and vacuolar degeneration in autopsied speciments of the ALS cases from the Kii Peninsula. These changes were previously thought to be unique to the Guam cases.

A collaborative study of lathyrism has been undertaken in India. This is pertinent because of the clinical consequences of chronic lathyrism (lateral sclerosis) and the possible implication of the cycad nut which can cause lathyrism in cases of ALS in the Marianas.

An excessive manganese content in the soil and water in Guam is the basis for emphasis on this metal and its possible effect in ALS. A manganese study in Guam suggested a possible concentration of cases of ALS and/or Parkinson's Disease among miners.

A recent study of environmental factors in the Mitogawa area has revealed a high content of manganese in soil and drinking water located in the area of mines which are currently not in use, and chemical analysis of rocks found in these mines showed a high concentration of manganese. Systematic chemical analysis of manganese in human nervous system tissues has been carried out by means of the neutron activation method. Normal distribution of trace metals including manganese in autopsied specimens of human brain have been found.

Parkinson's Disease

A most significant finding in the last two years has been the effectiveness of orally administered L-Dopa in the treatment of Parkinson's Disease. Of the first 100 treated patients reported on by one research center, 75% were improved from 20 to 100% in their disease symptoms. The greatest

effect was on rigidity and akinesia, though tremor was reduced as well. Improvement on most patients has extended up to 13 months and longer. It is clear that L-Dopa is unmistakably superior to any other drug heretofore available for the treatment of Parkinson's Disease. However, adverse reactions have appeared which restrict its clinical usefulness such as: nausea, vomiting, postural hypotension, cardiac dysrhythmias and involuntary movements. The relatively large doses necessary to achieve and maintain clinical improvement (up to 8 grams per day) has led to research for improved analogs or the combined use of L-Dopa with a decarboxylase inhibitor in an effort to more readily secure and maintain adequate levels of dopamine in blood and brain.

The therapeutic effectiveness of L-Dopa in Parkinson's Disease has raised the question of a disorder in catecholamine metabolism as an underlying cause. L-tyrosine, the immediate precursor of Dopa, does not improve the disease symptoms when administered. Studies in the turnover rate of labelled dopamine and norepinephrine do not indicate any disturbances in the metabolism of these amines, at least in extracerebral structures.

There are two predominant biochemical abnormalities in Parkinson's Disease. One is a decrease in dopamine, norepinephrine and serotonin in the basal ganglia and two, a decrease in neuromelanin in the substantia nigra.

A constant finding in both idiopathic and postencephalitic Parkinsonism is the degeneration of nerve cells in the nigra system and diminution of melanin in these nerve cells. The presence of neuromelanin appears to be essential for normal dopamine production in the substantia nigra and in Parkinsonism the melanin granules contain less melanin as compared to normal.

Chlorpromazine commonly produced Parkinsonism-like extrapyramidal symptoms and this may be related to the interaction of this drug with melanin in the substantia nigra or with an effect on catecholamine metabolism in the basal ganglia. Experiments have indicated that chlorpromazine stimulates melanization in certain cells, probably by activating tyrosinase which has been reported to be present in the substantia nigra. Theoretically, one might expect an activation of the substantia nigra tyrosinase to shunt tyrosine from the catecholamine pathway to the production of melanin. A reduction in dopamine in the nigra body would biochemically mimic changes in Parkinson's Disease.

It was the basic research on the biogenetic amines which led to the observation that dopamine was deficient in cells of the basal ganglia and hence to the trial first of dopamine and then of L-Dopa as a therapeutic agent. Various experiments have demonstrated that dopamine can produce marked increases in motor neuronal excitability and can enhance both flexor and extensor monosynaptic reflexes.

The chemical, dimethoxyphenylethylamine (DIMPEA) is of interest because it is considered to be a normal metabolite of dopamine and because of its possible relationship to Parkinson's Disease and mental illness.

Also in this regard is Mescaline 3, 4, 5-trimethoxyphenylethylamine. Both chemicals, when given by injection, produced a series of motor disturbances similar to those produced by cholinergic stimulation in the brain. DIMPEA was slightly less potent than Mescaline. Dopamine itself was found to be inactive in this regard; as was also homovanilic acid, the final metabolite of dopamine.

Convulsive Disorders

Epilepsy is a collective term applied to abnormal brain functions which are manifested in convulsive disorders. The spasms are characterized by sudden over-activity of the brain cells resulting in loss of consciousness, thought and self-control. The severity and longevity of the seizures depend upon the kind of epilepsy and the causes from which the disease has developed.

In epilepsy, known as "grand mal" the attack is most violent. The afflicted person may bite his tongue and invariably he loses control of his faculties. The recovery period is relatively long and requires a rest period after the attack is over. In "petit mal" the seizure is of a short duration, the attacks occur more frequently, sometimes as many as a dozen a day. Seizures are characterized by jerky movements of the muscles of the arms and neck. Included in this class are infantile spasms or quivering spells. If the area or areas of the brain can be located from which these abnormal electrical discharges emanate, the affliction is termed as "Focal" or Jacksonian" epilepsy. The seizure generally starts in the extremities and/or in one corner of the mouth. The affected part trembles violently. The trembling movement moves upwards. It either ends up in a minor seizure or the individual may lose consciousness just the same way as it happens in grand mal. By far the most common type of focal seizures is the one in which the discharging neurons exert their influence upon the metal processes as well as upon the muscles. The characteristic features of this type of "psychomotor epilepsy" are: sharp and sudden pain in the stomach, dreadful fear, flinging of arms aimlessly, smacking of lips, and other incoherent physical and mental behaviors. When a person regains his normal consciousness, the experience undergone during the attack is completely lost.

Epilepsy may be caused by several factors, such as brain damage, presence of a scar caused by a wound or an injury, drugs, congenital malformation, nutritional deficiencies, metabolic abnormalities, fever (in infants), infectious diseases (encephalitis, meningitis), brain tumors and abscesses. Heredity plays a very small role in the induction of epilepsy. If one twin develops epilepsy, the other one is likely to develop it also. However, parents with this disease do not necessarily have epileptogenic offspring.

The fundamental problem is to understand the basic mechanism involved in this disorder and to develop techniques to control it. A variety of techniques have been applied to the study of nerve cell activity. One important defect in epilepsy is the uncontrolled electrical discharge from nerve cells. A device know as the electroencephalogram (EEG) has been

developed which picks up electrical signals from the brain cells, amplifies them and records the impulses in the form of graphs. Electroencephalography is the most useful tool for both diagnosis and research. With its help electrical energy discharge patterns in groups of brain cells, and in various areas of the brain, are recorded. Also with the help of microelectrodes electrical activity of a single cell can be recorded.

Functionally, each neuron builds up a supply of electricity through the action of its metabolites. By repetitive activity of charge and discharge, the cells become overactive and fire off irregularly. The firing pattern may spread to other areas of the brain resulting in an epileptic seizure. When the neurons start firing again in harmony then the seizure is over. Brain waves so monitored give no indication of the individual's intelligence, thoughts, or his mental health. However, they provide strong clues as to whether or not a person has epilepsy. An EEG recorded during a seizure is likely to show unusually high bursts of energy release. The pattern indicates the type of seizure an individual has suffered.

Experimentally, epilepsy has been induced in animals with the use of various chemicals such as antibiotics (penicillin) and by the injection of metals and/or metallic oxides. Investigations with iron hydroxide, magnesium hydroxide, zinc oxide, chromium oxide, and mixed earth oxides showed that all these oxides or hydroxides are without epileptogenic effect when applied to the motor cortex of the monkey. On the other hand nickel and antimony proved most epileptogenic only when implanted as pellets into the motor cortex. Mild effects were observed with bismuth, zirconium, tin, titanium, molybdenum and tungsten. Twenty three more metallic powders have been tested on the sensorimotor cortex of monkeys. Some have shown very severe effects, while others remained ineffective.

Monkeys with temporal epileptogenic foci began to show seizures without loss of consciousness two months after the alumina cream was injected. Monkeys with an occipital focus had no clinical seizures, but developed EEG spikes in the ipsilateral occipital cortex a month after the alumina injection. The aim of these studies is to elucidate the neural mechanism involved in the transition of a localized lesion in the brain to an epileptogenic zone. This type of experimental approach has contributed new methods of inducing chronic epilepsy in animals which provides an important new tool for the study of this disease. Applying EEG techniques to these experimentally induced epileptic animals, efficacy of new drugs is being tested, epileptic loci (foci) have been determined, and new and improved surgical techniques for therapeutic application are being developed.

Treatment of epilepsy is concerned primarily with the medical and surgical approaches. Before surgery is performed, it is necessary to ascertain that the seizures originate wholly or in part from an area of the temporal lobes that can be safely removed without causing serious neurological damage; the seizures occur frequently and are incapacitating and presently available drugs are ineffective in controlling the seizures. Also, the surgery must be accomplished so as to avoid creating a secondary scar which

may in turn cause recurrence of the seizures.

Several physio-chemical differences between normal and epileptogenic tissues have been observed. Notable of these is that the tissue from the areas giving rise to abnormal electric discharge did not bind to itself nearly as much acetylcholine as did the normal tissue. This metabolite has been shown to occur in high quantities in epileptic regions of the brain. which suggests that when this substance accumulates, seizures result.

Nerve excitability is greatly influenced by variations in the chemical constituents of the fluids both inside and between the cells. Factors that modify the balance of these constituents, such as sodium and potassium, require a great deal more investigation. A series of amino acids, such as gamma aminobutyric acid (GABA), have been shown to be involved in the excitability of nerves. In this connection, a deficiency of vitamin B6 (pyridoxine) has induced seizures by producing a deficiency of GABA. Also a number of know convulsant toxins appear to interfere with the use of GABA in the body. Disturbances of electrolyte balance may be related to the common convulsion during fever in infancy. Information about the cause and correction of such disturbances may be applied to reduce the severity of recurrent epileptic attacks and to reduce the possibility of permanent brain injury which may be caused by such episodes.

Hypothermia (90° - 92° F) as a tool in therapy of patients with acute cerebral lesions such as; cerebral contusions, cranial hemorrhage, tumors and cardiac arrest has been tried. Patients that were in status epilepticus, or had intermittent seizures which could not be controlled by medication, were completely relieved of attacks or at least were benefited by cooling. Local cooling of the epileptic brain resulted in the suppression of spiking activity which also facilitated its response to anticonvulsant drugs. From this study it was concluded that hypothermia is another treatment for problems of status epilepticus where drugs are not effective or are contra-indicated. In this treatment no complications were observed that could be attributed to the hypothermia.

The treatment of epilepsy has depended to a major extent on drugs. One of the earliest medications, was a sedative called bromide. This was followed by another sedative, phenobarbital, which worked better but caused drowsiness in some cases. About twenty years ago diphenylhydantoin (Dilantin) was introduced in the treatment of epilepsy. It has been widely used and has proved to be a valuable anticonvulsant drug. However, it was soon recognized that ataxia sometimes occured as a complication of therapy with this drug. The ataxia may develop rapidly over a period of a few days or insidiously over weeks or even months. One unexplained feature about this ataxia is the fact that occasionally a patient will rapidly develop ataxia in spite of having taken the same dose of Dilantin for several years. It has been held that ataxia is a benign symptom only requiring a reduction in dosage or occasionally withdrawing of the drug. It was, however, later conclusively shown that cats subjected to Dilantin medication had developed severe loss of Purkinje cells in the cerebellum and cystic gliosis of the cerebellar white matter. A number of cases of permanent damage to the cerebellum, apparently

due to this drug, have also been reported.

Further investigation on the epileptic patients, who had suffered Dilantin intoxication indicated a high level of CSF protein levels during the period of intoxication. All the patients improved when the drug was withdrawn, but abnormal signs occasionally persisted for several months. Inhibition of the Na, K, Mg, ATPase enzyme system by Dilantin was observed which may be an important factor in causing neuronal damage. It is suggested that Dilantin intoxification may not be such a benign complication as was previously thought, but this still does not alter the fact that Dilantin is probably the most effective single drug presently available in the management of epilepsy.

The need of potent drugs of low toxicity is still paramount, especially in psychomotor epilepsy. The use of Dilantin, phenobarbital, primidone, and mephenytoin (Mesantoin) has left a relatively large group of inadequately responding patients. Recently considerable interest has been centered on the use of benzodiazepines in the treatment of epilepsy. Diazepam (Valium) has been proved to be effective in the interruption of epileptic seizures. Similarly, chlordiazepoxide (Librium) and especially nitrozepam (Mogadon) have been shown to be useful in prophylactic treatment.

Oxapepam (Serax) which is a metabolite of diazepam is easily absorbed from the intestines and is excreted quantitatively, or nearly so, as the glucuronide. Oxazepam has been widely used as an ataraxic because of the large safety ratic and the infrequent occurrence of side effects (drowsiness, ataxia, skin rash, headache, etc.). Clinical trial made it clear that Serax is a potent drug in the treatment of psychomotor epilepsy and is of low toxicity compared to Dilantin and other anticonvulsant agents. The effect is seen not only in the reduction of seizure frequency but also in the EEGs. The fact that this compound does not interact with Dilantin metabolism, facilitates its use in combination with Dilantin.

Investigations on convulsive disorders are supported by fifty-eight research grants amounting to $2,790,000.

Infectious Diseases

Infectious diseases of the nervous system include many types of illness and an equal number of research tools are employed to attack the problems. Epidemiological studies in man or animals frequently indicate whether a disease is infectious, how it is transmitted and perhaps some idea about the causative agent.

Methods most commonly employed for recognizing the presence of viral agents in cell cultures include: observations for cytopathic effects, hemagglutination, hemadsorption: interference, fluorescence and electron microscopies. With electron microscopy and immunological techniques, efforts are made to detect infectious agents. Immunofluorescent techniques are being used in diagnosing and studying brain inflammation due to viruses. Other studies are concerned with experimental encephalitis; the epidemiology of

Eastern equine encephalitis; the effects of parasites on the nervous system; testing vaccines for protection against arboviruses; and the possible role of viruses in acute neurological syndromes in children.

Other work that is being investigated includes: the after effects of infections during pregnancy where they may result in brain damage and mental retardation: analysis of viral polioencephalomyelitis in animals; an experimental measles encephalomyelitis; the mode and spread of a variety of neurotropic agents; and increasing research on the so called "slow virus" diseases which there is reason to believe may be especially important in a variety of diseases of the nervous system.

Several years ago a viral polioencephalomyelitis was identified in pigs. The virus has now been isolated from several different organs and has been shown to be an enterovirus quite unrelated to many other known viruses. All isolates but one produced polioencephalomyelitis in germ free pigs indistinguishable from naturally occurring infections.

Recently an agent causing paralysis of the CNS in rats has been isolated and is called hemorrhagic encephalitis of rats (HER). It produces acutely lethal encephalomyelitis when injected into suckling rats, including severe hemorrhagic lesions of the brain and spinal cord.

Transmission of encephalomyelitis from humans to animals and further from animal to animal, producing symptoms typical of subacute sclerosing panencephalitis (SSPE) syndrome in the animal, has provided an important new lead in isolating and understanding the causative agent in SSPE. This disease of children and young adults is characterized clinically by progressive intellectual deterioration, myoclonic jerks, and coma. The patients become severely emaciated and die from intercurrent infections. The diagnosis established during the incipient stages often shows a personality disorder or mental retardation. At that time the EEG shows slowing and dysrhythmia. However, high amplitude, low frequency synchronous waves do not develop until the patient exhibits myoclonic jerking. Spinal fluid proteins and cell counts remain normal or increase slightly during the entire course of the disease.

It has been suggested that SSPE is caused by an infection with measles virus. Indirect support has been derived from the close match between the curves representing the presence of measles antibodies in a non-selected population as a function of age, and the cumulative plot of the age of onset of SSPE. Since immunofluorescent studies seem to have ruled out the possibility of distemper virus, little doubt is left that SSPE is associated with the measles virus and the possibility that other etiological agents must be considered has become remote though not entirely disproven.

The most obvious question is concerned with the discrepancy between the clinical and pathomorphological expression of measles encephalitis and SSPE. The former is primarily an acute condition, sometimes fatal within twenty-four hours, which develops within a few days after, but sometimes prior to the exanthema. The latter runs an exceedingly chronic, remittent course with an insidious onset after the exanthema from four to seventeen

years with an apparent incubation period of eighteen months. Admittedly, this kind of measles encephalitis has not been proved to be due to a virus infection of the brain tissue. In fact, demyelination patterns together with the post-exanthematous onset have provided powerful arguments in support of an allergic encephalitic syndrome.

On the other hand, the so called incubation type of measles encephalitis manifested before the outbreak of the exanthema has always been interpreted as indicating a direct viral aggression against the brain. This view is supported by the experimental induction of clinical measles in animals five days after subcutaneous and intranasal inoculation with brain emulsion from a patient who died with acute measles encephalitis.

This comparative account illustrates that the difference between measles encephalitis and SSPE may be more apparent than real. One report indicates an instance of measles encephalitis which showed the classical features of SSPE years later.

A somewhat different aspect of the problem is provided by the concept of slow infections and slow viruses. Slow viruses are capable of producing an eminently chronic progressive disease following an incubation period of several years. This concept has been fruitful in respect to Visna, Scrapie, and Kuru. The inclusion of SSPE in this group finds support on clinical and patho-anatomical grounds. Just why the measles virus produced an acute encephalitis syndrome in some cases and behaves as a slow virus in another needs further intensive investigation.

Myxoviruses are medium sized, ether sensitive RNA viruses, which in man have the common effect of causing respiratory disease. Although they are not regarded as "neurotropic" viruses in man, mumps is the most common virus causing central nervous system infection in rodents. In these studies occasional neurons are infected by the unadapted strain and repeated passage has yielded a strain which infects parenchymal cells of the brain causing acute encephalitis. However, mumps virus in hamsters has been shown to cause a clinically inapparent infection limited largely to ependymal cells and neurons resulting in acute encephalitis.

Hydrocephalus may be caused by infectious agents contracted prior to birth. Suckling hamsters infected by mumps virus, developed a narrowing of the aqueduct of Sylvius and subsequently hydrocephalus. The narrowing of this canal responsible for draining the ventricles of the brain is the most common cause of hydrocephalus in man.

The study was conducted with experimental models to determine the histopathological changes in the brain during acute infection, and the aqueductal narrowing and hydrocephalus induction. The signs of clinical disease developed only after the resolution of the acute infection (about fourteen days) during which the lining cells of the aqueduct had been almost destroyed. Of the suckling hamsters inoculated with mumps virus, ninety-five percent developed clinical hydrocephalus. These and other histological changes were shown to be specifically related to the mumps virus infection.

Infection of human lymphocytes with herpes simplex virus apparently does not vary with the age of the host as it does in mouse macrophages. There was no obvious difference between the number of infected adult and neonatal cells. The addition of phytohemagglutinin greatly increased the number of infected cells in both types. Intramuscular inoculation of herpes simplex virus in rabbits failed to produce CNS disease. Intrasciatic inoculation caused hind leg paralysis with an ascending myelitis. However, unlike the neural spread in mice, no evidence of viral growth could be demonstrated in the nerve. This suggests a different mechanism of neural spread in different species. In a pilot study, rabbits immunized with herpes simplex virus survived a large dose of HFEM virus. Injection of adrenalin appeared to reactivate the virus with clinical signs of encephalitis in one month. A study of fixed rabies virus in mice showed that the infection was limited mostly to neurons of the rhinencephalic structures, brain stem nuclei, dorsal root ganglia, anterior horn cells, and cerebellar Purkinje cells. After subcutaneous inoculation of the virus, it spread rapidly to the CNS via peripheral nerves without evidence of infection of the endoneural cells or any extraneural tissues. Work with the Sindbis encephalitis virus in mice demonstrated a precipitous development of resistance during the second week of like, due apparently to a limitation in the spread of infection. No nonspecific viral inhibitors could be detected. Studies on mumps virus encephalitis in hamsters showed that disease and death resulted from the infection of neurons which remained morphologically normal. It is suggested that this material may be useful in investigating the "slow" viruses which seem to act in a similar way.

In Schilder's encephaloclastic sclerosis, virus-like particles were identified by electron microscopy which are distinctly different from those observed in the case with herpes simplex encephalomyelitis, but are similar to those that occur in subacute sclerosing leukoencephalitis. The nature of these virus-like particles is being investigated.

Investigations on infectious diseases of the nervous system are supported by thirteen research grants amounting to $550,000.

Cerebrovascular Disorders

In 1969 cerebrovascular research support approximated $5,407,000. This represented 95 grants, 19 of which are clinical research center grants, the remaining 76 research grants. The latter includes cooperative studies. Although individual researchers continue to pursue investigations in specific aspects of cerebrovascular disease, the main thrust of the Institute's program is in the clinical research centers, wherein teams of investigators representing basic scientists and clinical investigators coordinate and interrelate their efforts in laboratory and patient-oriented research. The number of clinical research centers has not increased in 1969 over 1968 but this should not necessarily be construed as a lack of interest. The rapid growth which made possible the establishment of 19 centers within 3-5 years more likely predicates that we may now be supporting the major clinical and basic research teams which can constitute a research center. The difficulty of attracting new young investigators to such centers remains a serious

problem as is the difficulty of establishing new research centers in institutions which have a small core or perhaps even only 1-2 investigators interested in cerebrovascular research.

Highlights of progress as reported from several of the research centers will be reported as examples of the ongoing activities in the centers. One center now in its third year of operation is making clinical and laboratory evaluations by a multidisciplinary group, which are focused through a specially designed environment-controlled dynamic angiography laboratory in an attempt to define the alterations of aortocranial hemodynamics that result during limb exercise and changes of head/body postural relationships; and the manner in which hemodynamics may be altered by other pathophysiologic and mechanical factors. They place special emphasis on the correlation of clinical information with the results of "radioisotope arteriography", cerebral perfusion estimates by inhalation and arterial injection of ^{133} Zenon, analysis of pulsations detected by ultrasound, catheter contrast aortography and angiography, and direct measurements of blood flow in extracranial arteries by electromagnetic flowmeters during reconstructive surgery. They hope by their studies to provide a base for development and evaluation of diagnostic tests, analyze and evaluate the results of treatment, and establish correlations of predictive values which may aid in the identification of stroke-prone individuals in large population groups. In their studies on the development of ultrasonic techniques for the investigation of cerebrovascular disorders, routine midline echoencephalography in three positions, which includes evaluation of pulsations and of ventricular size, is performed on all patients in the study. They are able to record simultaneously the pulsations from three separate areas of brain to relate the arrival delay at each point in reference to the R-peak of the ECG. Preliminary results indicate a direct temporal correlation between pulsation arrival and significant extracranial arterial stenosis. These studies will continue.

Another study being carried out at this center is on radioisotope arteriography to obtain estimates of regional blood flow. The potential of the system, a gamma (Anger) camera, multiparameter pulse height analyzer, and computer compatible magnetic tape, is being evaluated and on the basis of 1500 studies, it seems to be a highly effective tool with particular promise in the area of mass screening of patients with asymptomatic carotid bruits. Valuable information can be obtained concerning silent carotid artery stenosis and occlusion, occlusion of major leptomeningeal arteries and arteriovenous malformations, and when combined with rectilinear brain scans is a valuable adjunct in the differential diagnosis of positive brain scans due to tumor and infarction.

Another center reports the completion this year of a 4 bed intensive care unit and a monitoring systemfor ECG, EEG, respiration, blood pressure and temperature. It also includes alarms and the opportunity for automatically started continuous tape recording of cataclysmic events portended by changes in these parameters. A master control panel is provided at the nursing station, and O_2, CO_2 and suction are available at each bedside. Study of patients in the ICU are just beginning as a result of the availability of the ICU. On the other hand, it should be noted that difficulties are already apparent inasmuch as the availability of highly skilled specialty

nursing staff "around the clock" for research patients in the study poses logistical problems, the solutions to which are presently being sought. A clinical study is being developed to evaluate urokinase therapy in selected stroke patients. A protocol is being developed as are plans to obtain the necessary urokinase. Reports of progress will be made at a later date.

In this center as in others, the Anger camera is also being used to attempt a more detailed evaluation of cerebral blood flow. An interface is being built between the Anger camera and a PC computer which is currently being programmed to plot changing brain isotope content observed following the intra-arterial injection of inert gas to calculate and contour-plot regional cerebral flood flow in ml per 100 gms per minute. This group has been able to obtain a matrix of regional brain blood volume following intravenous administration of radioactive nondiffusible indicator. They plan to normalize the data and then assess regional alterations following photic stimulation.

Another study by this center relates to the work with radioactive oxygen-15. This is carried out by having the patient inhale air tagged with oxygen-15 once, and then following the rate of formation of water by brain tissue and the rate of equilibration of the tagged water thus formed with the body pool. Earlier, inhalation experiments were done almost exclusively but intra-arterial injections of blood tagged with oxygen-15 oxyhemoglobin gives a very similar picture in terms of the formation of water and the equilibration of water with body water. In patients with either vascular occlusive disease or with brain damage there has been a difference between the two hemispheres in almost all of the cases examined so far. During the past 6 months, this group has concentrated on building a special 6-probe collimated helmet that will allow the simultaneous measurement of identical points over 3 areas in each hemisphere. This has been used several times and the group reports excellent results. They hope that a more regional assessment of oxygen utilization can be made by this technique. The use of oxygen-15 presents some difficulties because of its high gamma value (511 Kev.).

Earlier annual reports refer to the variety and complexity of research problems to which the cerebrovascular clinical research centers address themselves. These problems by no means diminish in variety or complexity. Indeed, as investigations continue it becomes apparent that the complexities increase. Problems particularly relating to terminology, acceptance of specific definition of terms are of especial importance in insuring the relevance of results from one group in the hands of another group. For this and other important reasons, the annual workshops for program directors and selected staff of the research teams in the CV research centers becomes invaluable. The third workshop was held in January 1969. The indepth review was devoted to diabetes and the concurrent discussion groups were directed toward 1) Lipid Metabolism 2) Cerebral Arterial Spasm 3) Mechanisms in the Control of Cerebral Circulation and 4) Computer Retrieval of Neurologic Data.

It is now well-established that patients with severe hypertension are less likely to have strokes if their blood pressure is treated. There is little consensus when blood pressure is only moderately elevated or when it is intermittently elevated. Some evidence suggests that acute hypertension may actually induce cerebral arteriolar constriction and increase cerebral vascular resistance, or cause rupture of microaneurysms leading to a cerebrovascular syndrome. On the other hand, there exists opposition to antihypertensive therapy on the basis that the reduction of blood pressure in the face of arteriosclerotic cerebrovascular disease may induce cerebral thrombosis. The problem of whether treatment of mild cases of hypertension will prevent strokes or increase their frequency, especially in the elderly and arteriosclerotic, has never been established. There are two primary questions to be answered 1) Does drug treatment in moderate hypertension reduce the cerebrovascular recurrence rate? 2) Does blood pressure reduction influence prognosis? These are not necessarily the same questions unless one has the most accurate information possible concerning cooperation in taking medication and concerning the change in blood pressure induced.

The magnitude of the problem is substantial and requires the collective effort of neurologists and internists to arrive at some solution. The best way to solve this important therapeutic dilemma is by a cooperative (multi-institutional) clinical trial. For the past three and a half years, the National Institute of Neurological Diseases and Stroke has provided grant support for study of the long-term effect of a fixed antihypertensive therapeutic (thiazide plus rauwolfia) program on the recurrence rate of strokes in ambulatory patients with mild hypertension. Several types of strokes are included in the study, among them transient ischemic attacks and single completed episodes. Unbiased information concerning the possible deleterious effects of blood pressure lowering is being collected also, so that the precise advantages or limitations of antihypertensive therapy may be discovered. Eleven university clinics located in various parts of the United States are participating in this cooperative study. The treatment regime is consistent with that currently used in general practice and therefore generally applicable.

Preliminary studies indicate that 1) the incidence of cerebral thrombosis as well as cerebral hemorrhage can be reduced by effective long-term antihypertensive treatment; 2) cerebral atherosclerosis is not a universal prerequisite for an ischemic cerebrovascular episode; other factors favorably influenced by lowering the blood pressure may also play a role; and 3) the effects of antihypertensive therapy on stroke recurrence in cases of less severe hypertension require further study; therefore registration of new patients continues. It is anticipated that follow-up with replacement of losses will provide sufficient numbers of patients over a five-year period to answer the question posed, "Does the reduction of blood pressure affect the recurrence rate of stroke?" The investigators participating in the cooperative study believe that clear-cut answers may in some part become apparent.

At the present time antihypertensive therapy is used regularly without conviction. At the least, this cooperative study should provide data concerning the benefit or risk of prolonged lowering blood pressure in persons with cerebrovascular disease, at all levels of age and vascular deterioration.

Trauma (Head Injury)

In 1969, 50 research grants investigating specific problems in head injury were supported representing $1,900,000. Seven grants to develop head injury centers are now attacking problems in head injury in a multidisciplinary or multifaceted approach. The support for these centers approximates $826,653.

Examples of investigations being carried out in several of the centers will be described. One group is investigating the mass spectrometer on an experimental basis in animals as a means to obtain information regarding cerebral circulation in the presence of severe trauma. Studies have progressed to the point that instrumentation now being developed will make possible the application of the technic for human use. Problems have arisen in the development of a catheter suitable for human use with the mass spectrometer which is vacuum tight so that the entire molecular flow of gas will pass through the membrane. Experiments are under way to modify the intravascular catheter, resolving the apparent difficulties so that the investigations can be pursued in human trauma studies.

Another group reports that a two bed, head trauma unit has been completed for the study of seriously injured patients. Special equipment will make possible the observation of patients for the performance of certain studies, especially those related to blood gases. The relationship of pulmonary function to cerebral function and to recovery or lack of recovery of patients with serious cranio-cerebral injuries will be determined. Other studies are those related to patients who develop hemorrhagic pneumonia. The investigators' experience indicates that, if the pneumonia is not recognized during the first 24 hours after injury, it becomes intractable and often causes death. Severe pulmonary lesions may be present during the first 24 hours after injury and yet the clinical examination may be negative. Existence of the pneumonia has been indicated by determination of pO_2 and pCO_2 but the inadvertant administration of high concentrations of O_2 may cause capillary dilation and increase the tendency to hemorrhagic pneumonia. Alternatively excessive respiratory assistance may eliminate too much CO_2 and convert hypercarbia to hypocarbia. The investigative team proposes to carry out measurements of pulmonary and cardiac function within 24 hours of injury in order to understand the changes that underlie the development of hemmorrhagic pneumonia. This will lead to better methods for monitoring such patients so that optimal administration of O_2 and other therapy may minimize hemorrhagic pneumonia and increase chances of survival. Procedures to be used will include heart catheterization studies, measurement of blood gases, and radiologic methods such as angiography and scanning techniques. Particular attention will be given to measurements of pO_2, pCO_2, cardiac output, pulmonary artery pressure, and pulmonary arteriovenous shunts.

Another interesting study this group has underway is an assessment of the microbiologic flora in patients with head injury in order to determine changes that may occur and to relate changes in flora to the occurrence of clinically recognized secondary infection. To date 21 patients have been studied extensively. Organisms not ordinarily found have been identified,

and their frequency and sources tabulated. In 5 patients, illness was caused by abnormally occurring organisms, and in 10 others, illness from such organisms was suspected. Clinical illnesses included terminal sepsis in one patient and bacterial meningitis in another. By instituting careful procedures, secondary infections were reduced. It is anticipated that, by continuing investigation of sources and causes of secondary infections in patients with head injury, evidence for the need to control secondary infections may lead to significant increases of survival in these patients.

Experimental studies on the neurochemical alterations associated with head injury are continuing, the main emphasis being directed toward, a) chemical alterations in cerebral edema, b) metabolic changes in brain in acute edema, c) plasma and CSF lactate levels following head injury. The first two studies referred to are being carried out in animals, the last one both in animals and man. Methodology has been developed, and experimental studies have been initiated.

Another center is devoting its attention to laboratory and clinical studies of head injury with particular attention to the role of vascular changes in the production of cerebral edema, direct monitoring of intracranial pressure through ventricular drainage, the role of lesions in the region of the hypothalamus in the production of edema, beneficial effects of hemodilution, the use of the hyperbaric chamber in animal studies, as well as a number of other studies.

APPENDIX A

NUMBERS OF RESEARCH GRANTS SUPPORTED
IN FY 1969 AND AMOUNTS ARRANGED BY DISORDER CATEGORY

TYPE OF DISORDER	NO.	AMOUNT	% of $
ALL DISORDERS	1,798	$ 67,775,000	100
1. NEUROLOGICAL DISORDERS			
A. Chronic Neurological Disorders of Childhood	132	3,942,000	5.8
B. Chronic Neurological Disorders of Aging	60	2,371,000	3.5
C. Cerebrovascular Disorders	95	5,407,000	8.0
D. Epilepsy and Related Paroxysmal Disorders	65	2,274,000	3.4
E. Sclerosing Disorders	78	2,797,000	4.1
F. Muscular & Neuromuscular Disorders	152	5,013,000	7.4
G. Infectious Diseases	23	586,000	0.9
H. Accident and Injury	50	1,900,000	2.8
I. Tumors of Nervous System	41	982,000	1.4
J. General	360	12,200,000	18.0
ALL NEUROLOGICAL DISORDERS	1,056	$ 37,472,000	55.3

TYPE OF DISORDER	NO.	AMOUNT	% of $
ALL DISORDERS	1,798	$ 67,775,000	100
2. SENSORY & PERCEPTUAL DISORDERS			
A. Disorders of Vision	413	15,588,000	23.0
1. Cataract	(36)	(1,209,000)	(1.8)
2. Glaucoma	(35)	(1,176,000)	(1.7)
3. Retinopathy & Neurological Mechanism of Vision	(178)	(5,980,000)	(8.8)
4. Inflammatory & Parasitic	(52)	(2,388,000)	(3.5)
5. Metabolic & Degenerative	(14)	(569,000)	(0.8)
6. Strabismus & Neuromuscular	(28)	(941,000)	(1.4)
7. Injuries & Other Disorders including Tumors	(14)	(470,000)	(0.7)
8. General	(56)	(2,855,000)	(4.2)
B. Disorders of Hearing and Equilibrium	165	6,820,000	10.1
C. Disorders of Speech & Other Higher CNS Functions	33	1,991,000	2.9
D. Disorders of Other Senses	87	2,752,000	4.1
ALL SENSORY & PERCEPTUAL DISORDERS	698	$ 27,151,000	40.1
3. MULTI-CATEGORICAL	44	$ 3,152,000	4.6

May 15, 1969

Annual Report
Training Grants and Awards Branch, NINDS
July 1, 1968 through June 30, 1969

The extramural training program of the National Institute of Neurological Diseases and Stroke, formerly NINDB, includes three types of support. All funds are awarded on a competitive basis.

1. Graduate Training Grants provide funds to institutions for the establishment, improvement and support of broad, fundamental training in disciplines related to neurological, neuromuscular, sensory or communicative disorders. The primary objective of the program is to train additional needed clinical and laboratory teachers and investigators and community health and public health personnel. In addition, Special Fellowships (Traineeships) are awarded to provide individual stipend support to clinical and laboratory scientists for advanced, highly specialized research training in preparation for careers in research and academic medicine. Traineeships are awarded also to physicians for specialized clinical training to increase their expertise in the prevention, diagnosis and management of cerebrovascular disease.

2. Through Postdoctoral Fellowships, NINDS provides support to individual clinical and laboratory scientists for research training which follows immediately on receiving the doctoral degree.

3. Career Development Awards provide a substantial period of salary support for the young investigator, either clinical or laboratory, desiring experience and further training in an environment favorable to his establishment as a fully independent investigator and teacher.

NINDS has had primary research and research training responsibility for three broad categories of diseases and disorders--those relating to the central and peripheral nervous system, the communicative system and the visual system. There are, of course, areas of overlap among the three. After FY 1969, responsibility for a large majority of the grants and awards relating to vision will pass to the newly formed NEI.

Although each area has its distinctive training philosophy and needs for trained personnel, and therefore progress will be reported for each separately, certain problems are shared by all three.

The financial support afforded through the NINDS training grant and fellowship programs has played an important, if not essential, role in making it possible to establish an effective core of young basic and clinical scientists well-prepared for research and teaching in each of these three areas of medicine. Modest, but regular, budgetary increases in the past made this development possible.

It is ironic, then, that at the very point in time when manpower available to provide training leadership gives hope for approaching the needs of the next decade across the nation for competent teachers, researchers and physicians, the increases of financial support for training to make this possible have

virtually ceased.

Although in 1969, the Institute supported 310 training programs for a total of $16,929,000 all were supported substantially below the level recommended, and available funds did not allow the renewal of four approved programs nor the initiation of 17 new approved programs. In addition to 211 special fellowships (Traineeships) supported in 1968 for a total of $2,400,000 funds were not available to pay 34.

Postdoctoral Fellowships for $985,000 were awarded to 117 individuals in 1969, but there were 10 approved for whom funds were lacking.

Research Career Development Awards in 1969 were 94 in number for a total amount of $2,258,000, but 33 candidates approved with excellent priorities could not be paid.

Communicative Disorder Research Training

The number of training grants in the field of otolaryngology and in disciplines related to speech, hearing, and communicative disorders was increased by only two in 1969. Five additional approved grants went unfunded, and all 73 grants were funded in substantially lesser amounts than had been recommended, although costs of maintaining excellence in ongoing programs mount every year. Encouraging indications have appeared this year of increasing interest in training for investigative careers in the area of speech disorders, where problems are complex and training must be interdisciplinary.

Neurological Science Research Training

The number of training grants in the broad field of the neurological sciences was increased by only one over those supported in 1968. However, there were 11 new and two renewal approved applications which could not be paid from the funds available. All ongoing programs were paid in amounts reduced drastically from those recommended as reasonable to allow for satisfactory progress.

The trend noted in 1968 toward organizing training in the neurological sciences on an interdisciplinary basis has continued in 1969, with the submission of excellent training proposals embodying fresh, new approaches to the training of investigators and teachers.

Vision

There are three more training programs in the vision field in 1969 than there were in 1968 and an additional five could have been awarded, had the funds been sufficient. In this area also, the Institute was obliged to reduce grants to ongoing programs even below levels currently being received.

There has been a recent upswing in the number of programs which can provide training in ophthalmic pathology, largely because NINDB training grant and fellowship support in the past has increased the number of scientists specially prepared for research and teaching in this important but understaffed area of

vision research. This is the last year that training grants and fellowships in the field of vision will be a part of Institute responsibility. They will be transferred on July 1, 1969, to the new National Eye Institute.

Appendix A

Distribution, by Scientific Fields, of Training Grants Supported in Fiscal Year - 1969

Fields	No.	Amounts
Neurology	73	$ 5,208,000
Ophthalmology	56	3,205,000
Otolaryngology	49	2,864,000
Cerebrovascular	6	185,000
Communicative Disorders	8	362,000
Medical Audiology	9	374,000
Neuroanatomy	6	247,000
Neurobiology	2	40,000
Neurochemistry	2	133,000
Neuropathology	14	629,000
Neuropharmacology	4	232,000
Neurophysiology	13	682,000
Neuroradiology	9	254,000
Neurosurgery	25	888,000
Neurological Basic Science	3	150,000
Ophthalmic Pathology	1	49,000
Otolaryngology & Audiology	2	212,000
Pediatric Neurology	18	727,000
Sensory Physiology - Vision	3	151,000
Sensory Physiology - Oto.	1	20,000
Speech Pathology	3	234,000
Speech Pathology & Audiology	2	75,000
Vision Psychophysiology	1	8,000
TOTAL	310	$16,929,000

May 15, 1969

Appendix

Distribution, by Scientific Fields,
of Special Fellowships Awarded in FY 1969

Fields	No.	Amount
Audiology & Speech Pathology	7	$ 91,400
Biophysics	3	46,500
Cerebrovascular	1	15,500
Neuroanatomy	3	34,200
Neurobiology	2	18,200
Neurochemistry	7	88,600
Neuroendocrinology	2	26,400
Neurology	12	153,700
Neuropathology	21	210,600
Neuropharmacology	2	27,300
Neurophysiology	21	274,700
Neuroradiology	19	221,300
Neurosurgery	4	49,200
Neurovirology	3	37,400
Ophthalmology	36	397,000
Otolaryngology	4	47,500
Pediatric Neurology	28	339,600
Physiological Psychology	4	29,400
Sens. Physiology - Vision	9	112,000
TOTAL	211	$2,[illegible],000

May 15, 1969

Appendix C

Distribution, by Scientific Fields, of Fellowships Awarded in FY 1969

Fields	Research Career Awards		Research Career Development Awards		Postdoctoral Fellowships	
	No.	Amount	No.	Amount	No.	Amount
Audiology	1	$29,700	5	$112,700	-	----
Cerebrovascular	1	30,000	2	44,500	-	----
Neuroanatomy	2	43,100	1	17,800	6	48,000
Neurobiology	-	----	-	----	3	26,500
Neurochemistry	1	31,800	10	241,900	12	96,000
Neurocytology	-	----	4	86,500	7	61,000
Neuroendocrinology	1	26,000	-	----	4	29,700
Neurology	2	61,800	4	106,400	10	94,500
Neuropathology	-	----	6	141,300	3	24,000
Neuropharmacology	2	58,600	9	208,300	7	61,000
Neurophysiology	1	30,500	26	613,200	31	254,700
Neurosurgery	-	----	-	----	4	30,000
Neurovirology	-	----	3	65,800	2	16,900
Otolaryngology	1	32,400	-	----	1	10,000
Ophthalmic Pathology	-	----	3	67,000	3	26,000
Ophthalmology	1	32,400	5	152,300	8	70,300
Physiological Psychology	1	27,700	4	126,400	3	26,000
Sensory Physiol. - Vision	-	----	9	198,300	6	53,600
Sensory Physiol. - Oto.	-	----	3	75,600	5	40,000
Speech Pathology	-	----	-	----	2	16,800
TOTAL	14	$404,000	94	$2,258,000	117	$985,000

May 15, 1969

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